Official Title of Study:

An Open-label Extension Study to Assess the Long-term Safety, Tolerability, and Efficacy of KarXT in Subjects With DSM-5 Schizophrenia

NCT Number: NCT04659174

Document Date (Date in which document was last revised): 11 Jan 2022

16.1.1. Protocol and Protocol Amendments

The original protocol, version 1.0, dated 24 August 2020, was amended 3 times. The changes in each amendment are summarized in Section 9.4.1.

Protocols listed below are attached:

Protocol Version 1.0, Original protocol, dated 24 August 2020

Protocol Version 2.0, Protocol Amendment 1, dated 23 October 2020

Protocol Version 3.0, Protocol Amendment 2, dated 30 June 2021

Protocol Version 4.0, Protocol Amendment 3, dated 11 January 2022

1 FINAL CLINICAL STUDY PROTOCOL

Karuna Therapeutics

Protocol Title: An Open-label Extension Study to Assess the Long-term Safety, Tolerability, and Efficacy of KarXT in Subjects with DSM-5 Schizophrenia

Protocol Number: KAR-008

IND Number:	127471
EudraCT Number:	Not applicable
Name of Investigational Product:	KarXT
Phase of Development:	Phase 3
Indication:	Schizophrenia
Sponsor:	Karuna Therapeutics 33 Arch Street Suite 3110 Boston, MA 02110 Tel: [redacted] Email: [redacted]
Protocol Version:	1.0
Protocol Date:	24 Aug 2020

PROTOCOL APPROVAL SIGNATURES

Protocol Title: An Open-label Extension Study to Assess the Long-term Safety, Tolerability, and Efficacy of KarXT in Subjects with DSM-5 Schizophrenia

Protocol Number: KAR-008

This study will be conducted in compliance with the clinical study protocol (and amendments), International Council for Harmonisation (ICH) guidelines for current Good Clinical Practice (GCP), and applicable regulatory requirements.

Sponsor Signatory

[redacted]
Karuna Therapeutics

Signature: DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 8/25/2020 | 8:36:22 AM PDT

Date (DD-Mmm-YYYY): 8/25/2020 [redacted]

[redacted]
Karuna Therapeutics

Signature: DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 8/25/2020 | 8:34:25 AM PDT

Date (DD-Mmm-YYYY): [redacted]

Contract Research Organization Signatory

[redacted]
Syneos Health

Signature: DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I have reviewed this document Signing Time: 8/25/2020 | 8:38:36 AM PDT

Date (DD-Mmm-YYYY): [redacted]

Biostatistician

[redacted]
Kavanagh Statistical Consulting, LLC

Signature: DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 8/26/2020 | 5:53:19 AM PDT

Date (DD-Mmm-YYYY): 8/26/2020 [redacted]

INVESTIGATOR SIGNATURE PAGE

Protocol Title: An Open-label Extension Study to Assess the Long-term Safety, Tolerability, and Efficacy of KarXT in Subjects with DSM-5 Schizophrenia

Protocol Number: KAR-008

Confidentiality and Current Good Clinical Practice (GCP)/E6(R2) Compliance Statement

- I, the undersigned, have reviewed this protocol (and amendments), including appendices, and I will conduct the study as described in compliance with this protocol (and amendments), and relevant International Council for Harmonisation (ICH) guidelines including GCP and applicable regulatory requirements.
- I am thoroughly familiar with the appropriate use of the KarXT, as described in this protocol and any other information provided by Karuna Therapeutics including, but not limited to, the current investigator's brochure.
- Prior to initiating the trial, I will provide the independent ethics committee (IEC)/institutional review board (IRB) all items subject to review and will obtain a written and dated approval/favorable opinion. Once the protocol has been approved by the IEC/IRB, I will not modify this protocol without obtaining prior approval of Karuna Therapeutics and of the IEC/IRB. I will submit the protocol amendments and/or any informed consent form modifications to Karuna Therapeutics and the IEC/IRB, and approval will be obtained before any amendments are implemented.
- I ensure that all persons or party assisting me with the study are adequately qualified and informed about the Karuna Therapeutics KarXT and of their delegated study-related duties and functions as described in the protocol. I will supervise these delegated persons or parties in the conduct of this trial.
- I ensure that source documents and trial records that include all pertinent observations on each of the site's trial subjects will be attributable, legible, contemporaneous, original, accurate, and complete.
- I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all case report forms, laboratory samples, or source documents forwarded to the Sponsor. Clinical information may be reviewed by the Sponsor or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.
- Information developed in this clinical study may be disclosed by Karuna Therapeutics to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

<Name>

<Title>

Investigator Signature

Date (DD-Mmm-YYYY)

Institution

2 SYNOPSIS

Title of Study:	An Open-label Extension Study to Assess the Long-term Safety, Tolerability, and Efficacy of KarXT in Subjects with DSM-5 Schizophrenia
Protocol Number:	KAR-008
Investigators/Study Sites:	Approximately 30 study sites in the United States and 10 study sites in Ukraine
Phase of Development:	Phase 3
Objective(s):	**Primary Objective:** The primary objective of the study is to assess the long-term safety and tolerability of KarXT in subjects with a Diagnostic and Statistical Manual-Fifth Edition (DSM-5) diagnosis of schizophrenia. **Secondary Objective:** The secondary objective of this study is to assess the long-term efficacy and monitor trough concentrations of xanomeline and trospium after administration of KarXT in adults with a DSM-5 diagnosis of schizophrenia: • To evaluate the reduction in Positive and Negative Syndrome Scale (PANSS) total score • To evaluate the reduction in PANSS positive score • To evaluate the improvement in Clinical Global Impression-Severity (CGI-S) results • To evaluate the reduction in PANSS negative score • To evaluate the reduction in PANSS Marder Factor negative symptoms score • To measure trough concentrations of xanomeline and trospium after administration of KarXT in adults who are acutely psychotic with a DSM-5 diagnosis of schizophrenia **Exploratory Objective:** The exploratory objectives of this study are • To evaluate cognition with the Cambridge Neuropsychological Test Automated Battery (CANTAB) • To evaluate prolactin levels after administration of KarXT • To evaluate digital biomarkers of schizophrenia • To evaluate ecological momentary assessment (EMA) in schizophrenia • To evaluate cognitive insight
Study Endpoint(s):	**Primary safety endpoint:** The primary safety endpoint is the incidence of treatment-emergent adverse events (TEAEs) **Secondary safety endpoints:** The secondary safety endpoints of the study are: • Incidence of serious TEAEs • Incidence of TEAEs leading to withdrawal

	Secondary efficacy endpoints: The secondary efficacy endpoints of the study are: • Change from baseline in PANSS total score at Week 52 • Change from baseline in PANSS positive score at Week 52 • Change from baseline in PANSS negative score at Week 52 • Change from baseline in PANSS Negative Marder Factor score at Week 52 • Change from baseline in CGI-S score at Week 52 • Percentage of PANSS responders (a 30% change in PANSS total score) at Week 52 **Other Endpoints:** Safety endpoints: The other safety endpoints of the study are: • Spontaneously reported cholinergic symptoms • Change from baseline in Simpson-Angus Rating Scale (SAS) • Change from baseline in Barnes Rating Scale for Akathisia (BARS) • Change from baseline in Abnormal Involuntary Movement Scale (AIMS) • Change from baseline in body weight, body mass index (BMI), waist circumference • Change from baseline in orthostatic vital signs (supine and standing after 2 minutes): blood pressure (systolic and diastolic) and heart rate • Change from baseline in clinical laboratory assessments (hematology, clinical chemistry, coagulation, urinalysis, and drug screen) • Change from baseline in 12-lead electrocardiogram (ECG) • Change from baseline in physical examination • Suicidal ideation scale with the use of Columbia-Suicide Severity Rating Scale (C-SSRS) Pharmacokinetic Endpoint: The pharmacokinetic endpoint of the study is measurement of trough plasma concentrations of xanomeline and trospium. Exploratory Endpoints: The exploratory endpoints of the study are: • Change from baseline in cognition measuring core domains of impairment in schizophrenia using CANTAB • Change from baseline in prolactin levels • Observed digital biomarkers of schizophrenia • Observed EMA data over time in schizophrenia • Observed cognitive insight data over time
Study Design:	This is a Phase 3 multicenter, 53-week, outpatient, open-label extension (OLE) study to evaluate the long-term safety, tolerability, and efficacy of KarXT in subjects with DSM-5 schizophrenia who previously completed the treatment period of one of the two Phase 3 double-blind studies, KAR-007 or KAR-009. The study consists of a 52-week OLE treatment phase and a 7-day (±3 days) safety follow-up/end-of-study visit after the

	last KarXT dose for subjects who complete the treatment phase and those who prematurely discontinue from the study. After written informed consent, subjects who have completed the KAR-007 or KAR-009 Phase 3 acute study and received the last dose of the study drug in that trial will be rolled over in to the current OLE study. The assessments performed on Day 35 of Studies KAR-007 or KAR-009 will be considered as baseline assessments along with any additional assessments that will be performed on Day 1 of the current study. Consenting subjects who roll over into KAR-008 will have the previous blinded study medication discontinued and be dosed with a lead-in dose of open label KarXT the next day after completion of Visit 10 (Day 35) from the prior Study KAR-007 or KAR-009. The rollover is designed as above; a window extension is permitted but will need discussion with, and approval by, the medical monitor. Subjects who did not complete the full treatment period, or who early terminated Study KAR-007 or KAR-009, will not be eligible to enroll in this long-term extension study. A total of up to 350 subjects are planned to be enrolled in this study (aged 18 to 65 years) across approximately 30 study sites in the United States and 10 study sites in Ukraine. In this OLE study, all subjects will receive KarXT for up to 52 weeks. Regardless of treatment assignment in the preceding Phase 3 acute study (KAR-007 or KAR-009), all subjects will start on a lead-in dose of KarXT 50/20 (50 mg xanomeline/20 mg trospium) 2 times per day (BID) for the first 2 days (Days 1 and 2), followed by KarXT 100/20 BID for the remainder of Week 1 (Days 3 to 7). On Day 8, dosing will be titrated upwards to KarXT 125/30 BID unless the subject is continuing to experience adverse events (AEs) from the previous dose of KarXT 100/20 BID. All subjects who are increased to KarXT 125/30 BID, depending on tolerability, will have the option to return to KarXT 100/20 BID for the remainder of the treatment period. Re-escalation to 125/30 BID or re-titration in cases in which the subject has been off KarXT for a longer period of time (at least a week) is allowed and will require a discussion between the principal investigator and the medical monitor. Additional changes to KarXT dosing (e.g., temporary dose reductions) may be permitted as clinically indicated upon approval by the medical monitor. Beginning after Visit 5/Day 28, interim visits will be completed with flexibility between in-clinic visits, approximately once every 4 weeks. For interim visits, either a Home Health Care nurse or the study site staff will visit the subject to complete the scheduled visit. In addition to augment at-home visits, the telemedicine visit can be used. When needed, the sites will have the option to schedule a subject for an in-clinic visit. A safety follow-up/end-of-study/early termination visit (Visit 30/Day 371 ±3 days) will be performed for all subjects after the last dose of KarXT. An Independent Safety Monitoring Committee will be responsible for periodically reviewing the safety data from this study and confirming that the study may continue.
Number of Subjects:	**Inclusion Criteria:** Individuals must meet all of the following criteria to be included in the study:

	1. Subject is aged 18 to 65 years, inclusive. Exception: Subjects who turned 66 during KAR-007/009 participation will be eligible to continue in KAR-008. 2. Subject is capable of providing informed consent. a. A signed informed consent form must be provided before any study assessments are performed. b. Subject must be fluent in (oral and written) English (United States only) or local language (Ukraine only) to consent. 3. Subject has completed the treatment period on study drug (through Day 35 -2 days) of Studies KAR-007 or KAR-009. 4. Subject resides in a stable living situation, in the opinion of the investigator. 5. Subject has an identified, reliable informant/caregiver. An informant/caregiver is needed at the baseline visit as well as at the end of the study for relevant assessments. An informant/caregiver may not be necessary if the subject has been the patient of the investigator for ≥1 year. 6. Women of childbearing potential (WOCBP) or men whose sexual partners are WOCBP must be sexually abstinent (in line with their preferred and usual lifestyle) or willing and able to use at least 1 highly effective method of contraception during the study and for at least 7 days after the last dose of KarXT. Sperm donation is not allowed for 90 days after the final dose of KarXT. A female subject is considered to be a WOCBP after menarche and until she is in a postmenopausal state for 12 consecutive months or is otherwise permanently sterile (for which acceptable methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy). For the definition and list of highly effective methods of contraception, see Appendix 1. **Exclusion Criteria:** Subjects will be excluded from the study if 1 or more of the following criteria is/are applicable: 1. Risk for suicidal behavior during the study as determined by the investigator's clinical assessment and C-SSRS as confirmed by the following: a. Subject answers "Yes" to "suicidal ideation" Item 4 (active suicidal ideation with some intent to act, without specific plan) or Item 5 (active suicidal ideation with specific plan and intent) on the C-SSRS. b. Nonsuicidal self-injurious behavior is not exclusionary. 2. Any clinically significant abnormality, including any finding(s) from the physical examination, vital signs, ECG, or laboratory test at the end-of-treatment visit of Studies KAR-007 or KAR-009 that the investigator, in consultation with the medical monitor, would consider to jeopardize the safety of the subject. 3. Female subject is pregnant. 4. If, in the opinion of the investigator (and/or Sponsor), subject is unsuitable for enrollment in the study or subject has any finding that, in the view of the investigator (and/or Sponsor), may compromise the

	safety of the subject or affect his/her ability to adhere to the protocol visit schedule or fulfill visit requirements. 5. Subjects with extreme concerns relating to global pandemics such as coronavirus disease 2019 (COVID-19) that preclude study participation. 6. Risk of violent or destructive behavior. 7. Subjects participating in another investigational drug or device trial or planning on participating in another clinical trial during the course of the study.
Planned Sample Size:	A total of approximately 350 subjects (aged 18 to 65 years) are planned to be enrolled in this study.
Investigational Therapy:	1. Fixed dose KarXT 50/20 BID (50 mg xanomeline/20 mg trospium) oral (Days 1 to 2) 2. Fixed dose KarXT 100/20 BID (100 mg xanomeline/20 mg trospium) oral (Days 3 to 7) 3. Fixed dose KarXT 125/30 BID (125 mg xanomeline/30 mg trospium) oral (Days 8 to 364, if tolerated)
Reference Therapy:	Not applicable.
Treatment Duration:	Total study duration is up to 53 weeks, including a 52-week treatment phase and a 7-day follow-up/end-of-study phase.
Safety assessments:	Spontaneous AEs; serious AEs (SAEs) and AEs leading to discontinuation of the KarXT; cholinergic symptoms; SAS; BARS; AIMS; body weight; BMI; waist circumference; orthostatic vital signs; clinical laboratory assessments (hematology, clinical chemistry, coagulation, urinalysis, and drug screen); 12-lead ECG; physical examination; and C-SSRS will be evaluated throughout the study as scheduled.
Efficacy assessments:	PANSS total score, PANSS positive score, PANSS negative score, PANSS Negative Marder Factor score, and CGI-S score will be evaluated at scheduled visits.
Pharmacokinetic assessment:	Trough concentrations at scheduled visits.
Exploratory assessments	Cognition testing using CANTAB; prolactin levels; digital biomarkers of schizophrenia; EMA; and cognitive insight will be evaluated throughout the study as scheduled.
Statistical Methods and Planned Analyses:	Study Populations: <u>Enrolled population: All subjects who have given informed consent for KAR-008.</u> <u>Safety population</u>: All subjects who receive at least 1 dose of KarXT during the current study will be included in the safety population and will be used in the safety analysis. <u>Modified ITT (mITT) population</u>: All subjects who are enrolled, received at least 1 dose of KarXT during the current study, have a valid PANSS assessment at baseline of the acute study and at KAR-008 baseline will be included in the mITT population and will be used in the efficacy analysis. <u>PK population</u>: All subjects who have received at least 1 dose of KarXT and have at least 1 measurable plasma concentration in the current study will be included in the PK population.

	The primary safety endpoint of the study is the incidence of TEAEs. Secondary safety endpoints are the incidence of serious TEAEs and the incidence of TEAEs leading to withdrawal of KarXT. The secondary efficacy endpoints are change from baseline to Week 52 in the PANSS positive score, PANSS negative score, PANSS Negative Marder Factor score, CGI-S score, and the percentage of PANSS responders at Week 52. The exploratory endpoints of the study are change from baseline in cognition (CANTAB), prolactin levels, digital biomarkers, EMA, and cognitive insight. Descriptive statistics will be used to provide an overview of the safety and efficacy results. For continuous parameters, descriptive statistics will include n, mean, median, standard deviation, minimum and maximum; For categorical parameters, the number and percentage of subjects in each category will be presented. The denominator for percentages will be based on the number of subjects appropriate for the purposes of analysis. No statistical hypothesis testing will be performed.

3 TABLE OF CONTENTS

3.1 List of In-text Tables

3.2 List of In-text Figures

4 LIST OF ABBREVIATIONS

Abbreviation	Definition
AD	Alzheimer's disease
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
APD	antipsychotic drug
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{0-12}	area under the plasma concentration-time curve from 0 to 12 hours
AUC_{0-24}	area under the plasma concentration-time curve from 0 to 24 hours
BACS	Brief Assessment of Cognition in Schizophrenia
BARS	Barnes Akathisia Rating Scale
BID	twice daily
BMI	body mass index
BP	blood pressure
CANTAB	Cambridge Neuropsychological Test Automated Battery
CFR	Code of Federal Regulations
CGI-S	Clinical Global Impression–Severity
C_{max}	maximum plasma concentration
CNS	central nervous system
COVID-19	coronavirus disease 2019
C-SSRS	Columbia-Suicide Severity Rating Scale
CTS	clinical trial subject
DSM-5	Diagnostic and Statistical Manual–Fifth Edition
EDC	electronic data capture
ECG	electrocardiogram
EOS	end of study
EOT	end of treatment
ET	early termination
eCRF	electronic case report form
EMA	Ecological Momentary Assessment
EMAW	Ecological Momentary Assessment Wellness

Abbreviation	Definition
EPS	extrapyramidal symptoms
ET	early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
HIPAA	Health Insurance Portability Accountability Act
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	interactive web response system
IXRS	interactive response system
MCC	microcrystalline cellulose
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini International Neuropsychiatric Interview
mITT	modified intent-to-treat
MMRM	mixed model repeated measures
OLE	open-label extension
PANSS	Positive and Negative Syndrome Scale
PI	principal investigator
PK	pharmacokinetic(s)
SAS	Simpson-Angus Rating Scale
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Simpson Angus Scale
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TID	thrice daily
TK	toxicokinetic
T_{max}	time to maximum observed plasma concentration

Abbreviation	Definition
ULN	upper limit of normal
US	United States
VAS	visual analog scale
VCT	Verified Clinical Trials
VLMT	Verbal Learning and Memory Test
WOCBP	women of child bearing potential

5 INTRODUCTION

5.1 Background on Schizophrenia

Schizophrenia is a long-term mental disorder involving a breakdown in the relation between thought, emotion, and behavior, and leads to faulty perception, inappropriate actions and feelings, withdrawal from reality and personal relationships into fantasy and delusion, and a sense of mental fragmentation. Symptoms include delusions, hallucination, disorganized speech or behavior, and impaired cognitive ability.[1] The prevalence of schizophrenia is between 0.6% and 1.9% in the United States population.[2] Moreover, a claims analysis has estimated that the annual prevalence of diagnosed schizophrenia in the United States (US) is 5.1 per 1000 lives.[3] It is found equally in males and females, with males usually having an earlier onset of symptoms.[4]

Antipsychotic drugs (APDs) are the mainstay of treatment for schizophrenia.[5] All currently available antipsychotics act through blockage of all or subsets of dopamine receptors in the brain. First-generation APDs include chlorpromazine and haloperidol; treatment with these agents is marked by high rates of parkinsonian extrapyramidal symptoms (EPS) and tardive dyskinesia and they consequently have limited use today. The second-generation agents, that include risperidone, olanzapine, quetiapine, lurasidone, aripiprazole, and lumateperone, tend to have lower levels of EPS or tardive dyskinesia and are currently the most commonly prescribed APD class. However, the second-generation drugs also have problematic side effects that include significant weight gain, metabolic disturbances, sedation, and akathisia.[6, 7, 8] These side effects contribute to poor medication adherence resulting in frequent relapses and hospitalizations.[9, 10] Thus, there is a need for medications for schizophrenia which act through alternative mechanisms.

Central muscarinic receptors have been hypothesized to be therapeutic treatments for schizophrenia based on several converging lines of evidence including both animal and human studies.[11, 12] There are 5 subtypes of muscarinic receptors (M1-M5). The therapeutic effect of central muscarinic receptor agonism is thought to be due to agonism of M1 and M4 receptors in the central nervous system (CNS).[13] However, compounds that agonize M1 and M4 receptors are often not specific enough not to also agonize M2 and M3 receptors outside of the CNS due to the highly conserved allosteric binding sites that the receptors share, leading to adverse events (AEs) related to activation of these peripheral receptors. Thus, any potential benefit of muscarinic agonists in schizophrenia (or other indications such as Alzheimer's disease [AD]) has been outweighed by the occurrence of AEs associated with peripheral cholinergic side effects (nausea, vomiting, diarrhea, sweating, and excess salivation).

5.2 Background on KarXT (Xanomeline Tartrate and Trospium Chloride)

Xanomeline tartrate is a muscarinic-cholinergic receptor agonist. It has agonistic activity at all 5 muscarinic receptors, but preferentially stimulates M_1 and M_4 receptors and binding to M_1 and

M_4 receptors in the CNS, which is thought to be responsible for the drug's potential therapeutic effects (Roth, unpublished data). A recent study reports that xanomeline is a very potent M_4 muscarinic agonist in vivo, measured by various second messenger assays.[14] Xanomeline also enters the brain rapidly achieving a brain to plasma ratio of greater than 10 making it an attractive CNS drug candidate.[15]

Xanomeline does not have any direct binding activity on dopaminergic receptors, suggesting that its mechanism of action is unrelated to direct dopamine involvement.

Previous double-blind, placebo-controlled clinical trials have provided strong evidence that xanomeline has clinically relevant antipsychotic efficacy. In a multicenter outpatient trial in AD (N = 343), 3 doses of xanomeline (up to 225 mg/day) and placebo were assessed for 26 weeks.[16, 17] Significant dose-dependent improvements in psychotic symptoms relative to placebo were observed. Moreover, psychotic symptoms resolved quite rapidly in subjects who were symptomatic at baseline and a dose-dependent reduction in the emergence of psychotic symptoms versus placebo was also observed. In a completer analysis, cognitive improvement was also found suggesting longer treatment intervals may be necessary for cognitive enhancement.[16, 17] In a subsequent small (N = 20) double-blind, placebo-controlled inpatient trial in treatment-resistant subjects with schizophrenia, xanomeline (225 mg/day) demonstrated robust and relatively rapid improvement in psychosis compared to placebo. In addition, improvement in both negative symptoms and cognitive impairment was observed.[18]

In both the AD and schizophrenia trials, as well as in previous healthy volunteer studies, dose-dependent "cholinergic" AEs were also reported, namely vomiting, nausea, diarrhea, sweating, and hypersalivation. These side effects were frequent and, at the higher doses of xanomeline, led to significant rates of discontinuation in the AD studies. This "cholinergic" AE profile curtailed further development of xanomeline as a single agent.

It is believed that the procholinergic AEs associated with xanomeline are mediated by xanomeline's stimulation of *peripheral* rather than *central* muscarinic receptors, which would make these AEs theoretically amenable to counteracting peripheral anticholinergic treatment. Trospium chloride is a peripherally acting muscarinic antagonist which binds to and antagonizes all 5 muscarinic receptor subtypes.[19] It is a commonly used generic drug approved for over 10 years by the US Food and Drug Administration (FDA) and by European authorities to treat overactive bladder and is generally well tolerated.[19] Several human subject studies have demonstrated that trospium does not appreciably cross the blood-brain barrier, consistent with the drug's quaternary ammonium structure.[20]

KarXT is a novel combination of xanomeline tartrate and trospium chloride. Karuna hypothesized that the addition of trospium would mitigate peripheral pro-cholinergic side effects (vomiting, nausea, diarrhea, sweating, and hyper-salivation) and thus provide a strategy to allow xanomeline to be administered and stimulate brain muscarinic receptors with a decreased side

effect burden. Phase 1 studies in healthy volunteers of this combination demonstrated that KarXT reduced these side effects by 46% compared to xanomeline alone.[21] Moreover, the remaining cholinergic AEs were generally mild to moderate in severity and transient in nature, often lasting a few hours without recurrence and were generally single-episode. In general, KarXT was well tolerated in healthy adult volunteers. These encouraging safety data prompted further work to assess KarXT for the treatment of schizophrenia and potentially other CNS disorders.

Karuna has recently completed an adequate and well-controlled, randomized, multi-center Phase 2, placebo-controlled, inpatient clinical trial of acute psychosis with schizophrenia in 182 adult subjects (KAR-004). KarXT demonstrated a statistically significant and clinically meaningful 11.6 point mean reduction in total Positive and Negative Syndrome Scale (PANSS) at 5 weeks compared to placebo ($p < 0.0001$), with statistical separation at each time point assessed (2, 4 and 5 weeks), and also demonstrated good overall safety and tolerability.

The purpose of the current study is to evaluate the long-term safety and tolerability of KarXT (xanomeline 125 mg/trospium 30 mg) administered twice daily (BID) in adult outpatients with Diagnostic and Statistical Manual–Fifth Edition (DSM-5) diagnosis of schizophrenia.

Xanomeline is currently not approved or marketed in any country. Trospium is marketed in the US and other regions of the world for the treatment of overactive bladder.

5.2.1 Nonclinical Studies

The following is a summary of the important nonclinical safety and toxicology studies. More detailed information can be found in the KarXT Investigator's Brochure (IB).

The acute toxicity of xanomeline tartrate was evaluated in mice and rats. All animals were observed for 2 weeks for mortality and clinical signs of intolerance, and then necropsied for gross examinations. In-life findings attributed to the test article included excessive muscarinic-mediated pharmacology, such as excessive salivation, hypoactivity, ataxia, soft stools, exophthalmos, ocular discharge, tremors, and convulsions, with survivors typically appearing normal by Day 3 or Day 4. Gross findings at necropsy were generally unremarkable (eg, gas-distended or mucous-filled gastrointestinal [GI] tracts after oral dosing).

KarXT-301 was a 14-day, repeat dose study of KarXT in rats where relatively high doses of xanomeline and trospium were given, with either xanomeline alone or in combination with trospium. Seven groups of 10 rats/sex/group were administered either vehicle (reverse osmosis water), xanomeline alone at 37, 75, 150, or 300 mg/kg/day (split into BID doses, every 12 hours), or xanomeline/trospium combination doses of 150/200 mg/kg/day or 225/400 mg/kg/day, respectively (split into BID doses, every 12 hours).

Satellite animals were included for the collection of plasma after the first and last doses for the determination of drug concentrations of each parent drug in support of toxicokinetic (TK) assessments.

There was no target-organ toxicity revealed by clinical pathology or by gross or microscopic assessments. All intolerance could be attributed to recognized pharmacology of either test article. No dose-related ophthalmic observations were noted. Findings were not indicative of specific target organ toxicity. In short, no new hazard was identified.

Clinical observations noted in most animals administered 300 mg/kg/day xanomeline included hypoactivity, clear oral discharge, dilated pupils, irregular or labored respiration, and rough haircoat, among other observations. These findings are generally consistent with the anticipated pharmacology of xanomeline.

Three TK animals in the low-dose combination group died or were euthanized in extremis. It is unclear to what extent the combination treatment effects versus the different handling of these animals (including 3 plasma samplings per animal) contributed to these deaths. If gavage accidents were involved (as happened with some TK animals), then they were not detected at gross necropsy. There was no microscopic evidence of toxicity seen in any toxicity animals in this group or in the higher-dose combination group.

Three toxicology and 3 TK animal deaths (total of 6) occurred in the high-dose combination group. Two toxicology animals had evidence of gavage accidents. For the third, the cause of death was undetermined, and a test article-related effect cannot be ruled out, but esophageal muscular degeneration/regeneration is indicated in some dosing-related trauma. If gavage accidents were involved, then they were not detected at gross necropsy. There was no evidence of target organ microscopic findings in GI tract or any other tissue of any animal, including the early death toxicity animals.

A pharmacodynamics (PD)-mediated reduction in GI motility is consistent with the anti-muscarinic effects of trospium on intestinal musculature. Fecal retention, malabsorption, cessation of eating, dehydration, and rapid deterioration followed with continued dosing. Cessation of dosing in the high-dose combination animals that survived led to rapid recovery, implying the deleterious effects had been PD-related. No effects on food consumption were seen in any xanomeline-alone group. The lack of microscopic findings in the GI tract of any early death or surviving animal implies that the adverse effects were pharmacologically mediated rather than direct target organ toxicity.

Twenty-eight Day Repeat-Dose Studies with Xanomeline in Rats and Monkeys: Rats were fed xanomeline tartrate at 0, 0.05, 0.1, or 0.2% daily and monkeys were fed xanomeline tartrate daily at 0, 5, 12.5, or 30 mg/kg. All animals survived until necropsy. Safety findings in rats included reduced body weight in the high-dose group, increases in gamma-glutamyl-transferase, cholesterol, and bilirubin, slight decreases in triglycerides, bile duct hyperplasia, higher serum potassium (males), and lower serum globulin (females). Findings in monkeys were dose-related and included signs of intolerance such as emesis, salivation, diarrhea, hypoactivity, weight loss, and treatment-related tachycardia in the high-dose animals.

Forty-Day Repeat Dose Study of KarXT in Rats (KarXT-302): Six groups of 15 rats/sex/group were given vehicle, xanomeline alone at 75 or 150 mg/kg/day, trospium alone at 100 mg/kg/day, or xanomeline/trospium combination at doses of 75/50 mg/kg/day or 150/100 mg/kg/day, with all doses split into BID doses. Satellite rats (TK animals) were included for collection of plasma after the first and last doses to determine concentrations of each drug. Dosing was initially planned to be 90 days, but was terminated after 40 days because of unexpected deaths in the TK animals. No target organ toxicity was seen. Safety findings included pharmacologically mediated constipation in the trospium alone and combination groups, and mild biliary hyperplasia in the high-dose xanomeline-alone and combination groups. There were 4 unscheduled deaths in TK animals; 2 in the high-dose xanomeline-alone group (150 g/kg/day) and 2 in the high-dose combination group (150 mg/kg/day xanomeline plus 100 mg/kg/day trospium). Both xanomeline-only animals had necropsy gross findings of a gavage accident and cause of death could not be determined. All toxicology animals survived to their scheduled sacrifice. The Sponsor considers that the volume depletion and trauma of multiple bleeds (3 per animal) followed by reduced absorption of fluids and nutrients secondary to reduced GI motility with continued BID dosing, explains the greater demise of TK animals relative to toxicity animals.

Based on the results of the 90-day rat toxicology study, oral administration of trospium chloride and xanomeline tartrate alone or in combination to Crl:CD(SD) rats BID (12 hours ±60 minutes apart) at dosage levels of 25 and 50 mg/kg/dose trospium chloride, 37 and 75 mg/kg/dose xanomeline tartrate and a combination of 37/25, 75/25, and 75/50 mg/kg/dose xanomeline tartrate/trospium chloride for a minimum of 90 days resulted in minimal to moderate bile duct hyperplasia in the livers of the xanomeline tartrate and combination (xanomeline tartrate and trospium chloride) group males.

Although there were no notable differences in the incidence of bile duct hyperplasia when comparing the single vs combination groups, there was an increased severity observed in the combination group males (specifically the 75/25 and 75/50 mg/kg/dose combination group males) when compared to the xanomeline tartrate group males at the terminal euthanasia. The bile duct hyperplasia was considered adverse in the high-dose xanomeline tartrate group males and in the 75/25 and 75/50 mg/kg/dose combination group males due to instances of moderate severity. Therefore, the no-observed-adverse-effect level was considered to be 50 mg/kg/dose for trospium chloride, 37 mg/kg/dose for xanomeline tartrate, and 37/25 mg/kg/dose for the combination of xanomeline tartrate/trospium chloride. At these doses for males, mean plasma AUC_{0-24} values were 27,700 pg•hr/mL for trospium, 146,000 pg•hr/mL for xanomeline, and 4510 + 111,000 pg•hr/mL for trospium + xanomeline, respectively, on Day 91.

At these doses for females, mean plasma AUC_{0-24} values were 9230 pg•hr/mL for trospium, 267,000 pg•hr/mL for xanomeline, and 16,700 + 171,000 pg•hr/mL for trospium + xanomeline, respectively, on Day 91. The absence of bile duct hyperplasia in females cannot be explained from differences in drug exposure. At the recovery euthanasia, bile duct hyperplasia was still present, but was limited to minimal severity and there was a decreased incidence in both the

xanomeline tartrate and combination group males. There was also no notable difference in severity between the single vs combination groups at the recovery euthanasia. Given the decreased incidence/severity, in combination with the improved histologic appearance of bile ducts at the recovery euthanasia (ie, smaller/flattened epithelium, non-inflammatory, and an absence of portal bridging), changes at the recovery euthanasia were consistent with a partial resolution of bile duct hyperplasia. With an absence of correlating serum liver enzyme elevations, bile acid alterations or hepatocellular degeneration, necrosis or regeneration, and with the apparent reversibility following cessation of treatment, these findings appear to have been tolerable by the affected animals. Therefore, the maximum tolerated dose was considered to be 50 mg/kg/dose for trospium chloride, 75 mg/kg/dose for xanomeline tartrate, and 75/50 mg/kg/dose for the combination of xanomeline tartrate/trospium chloride.

For males, corresponding mean plasma AUC_{0-24} values were 27,700 pg•hr/mL for trospium, 822,000 pg•hr/mL for xanomeline, and 133,000 + 276,000 pg•hr/mL for trospium + xanomeline, respectively, on Day 91. For females, corresponding mean plasma AUC_{0-24} values were 9230 pg•hr/mL for trospium, 2,090,000 pg•hr/mL for xanomeline, and 17,600 + 950,000 pg•hr/mL for trospium + xanomeline, respectively, on Day 91.

In summary, no new "combination" findings were discovered; toxicology studies revealed the familiar exaggerations of systemic and CNS muscarinic effects that had previously been seen with xanomeline or trospium at high doses. Target organ findings with xanomeline alone were limited to biliary hyperplasia in the 28-day rat study but not the 28-day or 12-month monkey study, though similar findings were described in a 6-month monkey study. With KarXT, biliary hyperplasia was not observed in the 14-day rat study but was reported in the 40-day rat study. Notably, these hyperplastic findings are not thought to represent pre-neoplastic lesions, because they were of low severity; no fibrosis or associated hepatocellular changes, and no significant effects were seen on hepatobiliary-related serum chemistry.

5.2.2 Completed Clinical Studies

Refer to the IB for complete information regarding previous clinical studies conducted with xanomeline by Eli Lilly, and studies KAR-001, KAR-002, KAR-003 and KAR-004 conducted by Karuna Therapeutics using xanomeline with trospium.

To date, more than 750 subjects or volunteers have been exposed to xanomeline tartrate (oral formulation, either alone, in combination with trospium, or as the combination drug KarXT) in 18 completed clinical studies conducted either by Eli Lilly or Karuna Therapeutics, some for as long as 3 years. In those studies, significant improvements in cognition and reduced psychotic symptoms were observed.

A study of xanomeline monotherapy in subjects with schizophrenia was reported in 2008.[18] In this pilot study, the effects of xanomeline were examined in 20 schizophrenia subjects utilizing a double-blind, placebo-controlled, 4-week study design. Subjects treated with xanomeline did significantly better than subjects in the placebo group on Brief Psychiatric Rating Scale total

scores and PANSS total scores (ie, 24-point change over placebo, p = 0.04). In the cognitive test battery, subjects in the xanomeline group showed improvements relative to placebo in some of the cognitive domains of verbal learning and short-term memory function. These studies demonstrated the potential for xanomeline as a treatment for psychosis and cognition across multiple subject populations.

Study H2Q-EW-E001, conducted by Eli Lilly, had 36 male healthy volunteers in 4 groups of 9, who were administered escalating single doses of xanomeline tartrate in increments of 1, 5, 10, 25, 50, 75, 100 and 150 mg. Each group took 2 ascending doses of xanomeline tartrate and 1 dose of placebo in a single subject blind manner. There were no serious AEs (SAEs). Adverse events included watery diarrhea, nausea, dizziness, sweating, shivering, mild disorientation, increased blood pressure (BP), increase(s) in sitting and standing heart rate, slight increase in supine systolic BP, and postural hypotension.

The clinical experience with KarXT initiated by Karuna Therapeutics to date includes 3 completed Phase 1, clinical pharmacology studies in healthy volunteers (KAR-001, KAR-002, and KAR-003) and one completed Phase 2 study (KAR-004) in adult inpatients with DSM-5 schizophrenia.

The first study conducted by Karuna, KAR-001 was a Phase 1, double-blind, randomized, multiple-dose, pilot study comparing xanomeline administered alone to xanomeline administered in combination with trospium chloride in normal healthy volunteers. This study consisted of 2 arms, in which xanomeline was administered three times daily (TID), alone, at a total daily dose of 225 mg in 1 arm, and the second arm received the same dose of xanomeline in combination with trospium chloride 20 mg administered BID, a total daily dose of 40 mg. Subjects were treated for 7 days. The goal was to determine whether this dosing regimen would reduce the cholinergic side effects of xanomeline by co-administration of the muscarinic antagonist, trospium.

Overall, treatment with xanomeline 225 mg daily + trospium 40 mg daily administered over 7 days was considered safe and well tolerated. The results of key and supportive endpoints showed a numerical reduction (although not statistically significant) in visual analog scale (VAS) scores for cholinergic events for the xanomeline + trospium treatment arm compared to the xanomeline-alone treatment arm. Specifically, consistent numerical reduction in VAS scores for the xanomeline + trospium treatment arm was observed for the supportive endpoints of maximum weekly individual VAS scores and mean daily maximum composite VAS scores.

Results of the clinician-administered scales were supportive of a reduction in vomiting, feelings of nausea, excess salivation, and sweating that interfered with daily activities in the xanomeline + trospium treatment arm compared to the xanomeline-alone treatment arm.

There were no meaningful differences between treatment groups in heart rate, resting BP, orthostatic BP or any electrocardiogram (ECG) parameters including QT. A small subset of subjects in both treatment arms had transient increases in heart rate and orthostatic BP changes

which may have contributed to syncope and postural dizziness in those subjects. Two subjects (both in the xanomeline-alone arm) experienced syncope. The incidence of orthostatic AEs in the KarXT group was approximately one-half that of subjects in the xanomeline-alone group.

The most commonly reported treatment-emergent AEs (TEAEs) in KAR-001 (≥20% of subjects in either treatment arm) were hyperhidrosis, salivary hypersecretion, nausea, dizziness postural, and diarrhea. Subject incidences of these 5 TEAEs was higher in the xanomeline-alone treatment arm (61.8%) compared to the xanomeline + trospium treatment arm (34.3%).

Overall, treatment with xanomeline 225 mg combined with trospium chloride 40 mg administered over 7 days was considered safe and well tolerated. The observed side effect profile was consistent with the known safety profile of xanomeline and trospium chloride. The incidence of TEAEs and cholinergic TEAEs was lower in the xanomeline + trospium treatment arm compared to the xanomeline-alone treatment arm.

Study KAR-002 was a Phase 1, double-blind, randomized, multiple-dose adaptive design pilot study to evaluate the safety and tolerability of KarXT in normal healthy volunteers. Subjects received either 100 mg xanomeline + 20 mg trospium BID or placebo. The first cohort of this study was stopped after 1.5 days when the FDA put the program on hold due to a preliminary rat finding in the 14-day study. This study used a new formulation of KarXT in which xanomeline and trospium were combined into a single dose form and given BID. Safety findings included an increase in orthostatic complaints. Caution should be used in drawing conclusions from this study, as subjects did not have time to reach steady state plasma levels from dosing, as only 3 doses were given.

Study KAR-003 was a Phase 1, double-blind, randomized, multiple-dose, adaptive design, inpatient pilot study to evaluate the safety and tolerability of KarXT in normal healthy volunteers. The primary objective of this study was to assess the safety and tolerability of 7 days of daily administration of KarXT at various dose combinations, administered BID. Subjects received either KarXT or placebo (3:1 ratio). All subjects on KarXT received 2 days of 50 mg xanomeline + 20 mg trospium BID, and then increased to different doses for Days 3 to 7. This study also used the new formulation of KarXT in which xanomeline and trospium were combined into a single dosage form and given BID.

There was a relatively high degree of variability in xanomeline and trospium exposures between individuals in all cohorts, which is consistent with previous results with KarXT, xanomeline-alone, and trospium-alone. Peak plasma concentrations were observed at a median time of 2.0 hours for xanomeline and 1.0 hour for trospium across all treatment groups and study days.

Although there was insufficient data to draw a definitive conclusion regarding the impact of trospium on the pharmacokinetics (PK) and bioavailability of xanomeline, or the impact of xanomeline on the pharmacokinetics and bioavailability of trospium, the PK results suggest that neither drug had a meaningful impact on the PK behavior of the other drug.

During the 2-day lead-in phase, the most common AEs (≥20% of subjects) when all the subjects completed dosing were dry mouth, nausea, and constipation. For the treatment groups that completed dosing, although the incidence of TEAEs was lower in the KarXT 100/20 BID (66.7%) group compared to KarXT 125/40 group (88.9%), the incidence of cholinergic TEAEs (nausea, vomiting, diarrhea, sweating, and excess salivation) was similar between the 2 groups. The most commonly reported TEAEs (≥20% of subjects in either treatment group) in these groups were dizziness, nausea, dry mouth, headache, vomiting, dyspepsia, somnolence, vision blurred, and dysuria. For the treatment groups that did not complete dosing (KarXT 150/20 BID group and KarXT 150/40 BID group), the cholinergic TEAEs were generally higher compared to the treatment groups that completed dosing.

Overall, anticholinergic TEAEs appeared to occur primarily in the treatment groups that were dosed with 40 mg trospium BID (KarXT 150/40 BID and KarXT 125/40 BID groups), particularly when paired with 125 mg xanomeline BID, suggesting to consider slightly lowering the trospium dose from 40 mg BID in future studies. All TEAEs were mild or moderate in severity, and there were no SAEs or deaths. Treatment-emergent AEs were primarily cholinergic or orthostatic (and a few anticholinergic). Doses of 100 mg and 125 mg BID of xanomeline were well tolerated when paired with 20 mg and 40 mg BID of trospium, respectively. The safety and tolerability profile of KarXT 100/20 BID and KarXT 125/40 BID was acceptable and supports further evaluation at similar doses in future studies. Doses of KarXT 150/20 BID and 150/40 BID were not well tolerated in this study. A pairing of 150 mg xanomeline with 40 mg trospium appeared to be better tolerated than 150/20, but some subjects still experienced tolerability issues.

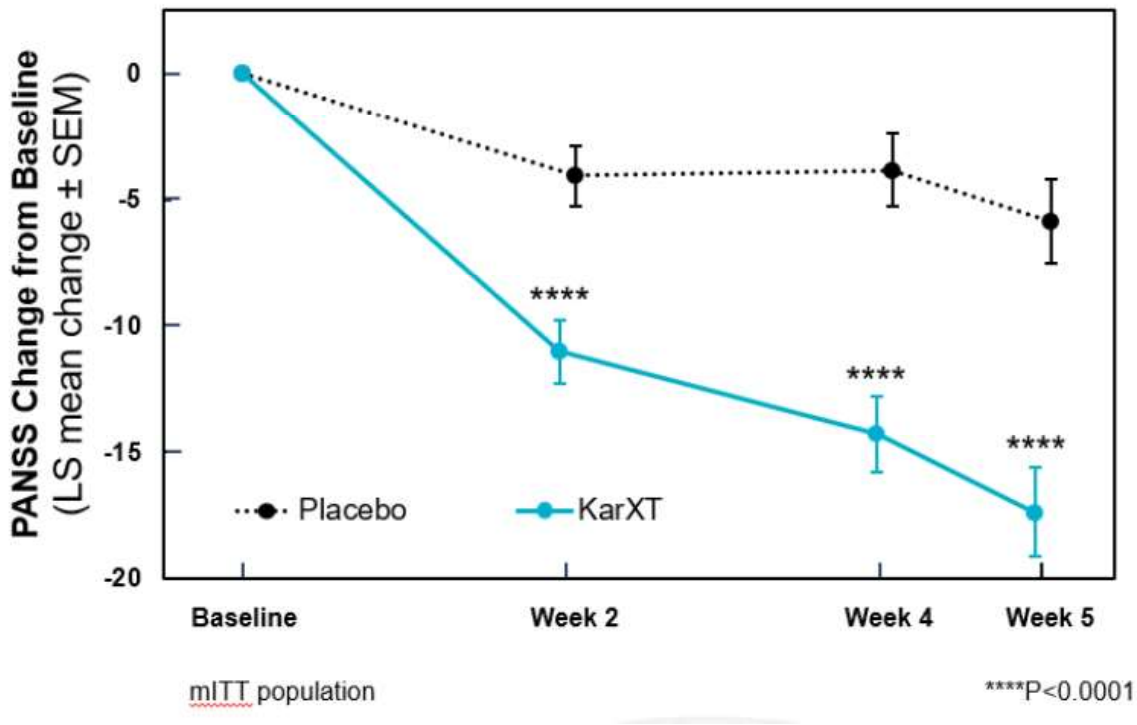
Study KAR-004 was a Phase 2 randomized, double-blinded study to assess the safety, tolerability, and efficacy of KarXT in adults with DSM-5 schizophrenia, hospitalized with acute psychosis. The primary objective of the study was to assess the efficacy of KarXT (125/30 BID) versus placebo in reducing PANSS total scores in adult inpatients with a DSM-5 diagnosis of schizophrenia. Subjects received either KarXT or placebo (1:1 ratio) for a treatment period of 5 weeks. All subjects on KarXT received a lead-in dose of KarXT 50/20 BID for the first 2 days followed by KarXT 100/20 BID on Days 3 to 7. On Day 8, dosing was titrated upwards to KarXT 125/30 BID unless the subject was continuing to experience AEs from a previous dose increase of 100/20 BID. The clinical portion of this study was completed and the clinical study report is in progress. No new safety concerns have arisen during this study.

The KAR-004 trial results are unambiguous regarding efficacy, where not only the primary outcome measure showed a robust separation from placebo, but the additional sensitivity and secondary outcome measures were consistently robust as well.

KarXT demonstrated statistically significant and clinically meaningful mean reductions in total PANSS scores at 5 weeks compared to placebo ($p < 0.0001$) in the modified intent-to-treat (mITT) population. The KarXT group showed an adjusted mean improvement of 17.40 points at Week 5 compared to an adjusted mean 5.85 point improvement in the placebo group for a

difference of 11.56 points in the total PANSS score (Figure 1). Substantial significant differences were also seen between KarXT and placebo at Weeks 2 and 4; moreover, the difference appeared to be widening with each successive time point. In addition, sensitivity analyses of the primary outcome measure all showed the same strong differences from placebo attesting to the robustness of the finding in Completer, last observation carried forward, and Per Protocol populations (all with p<0.0001). Also, analyses exploring missingness via imputation for missing data at random or not missing at random also showed strong separation (both with p<0.0001). The Cohen's d effect size observed in this trial was 0.75.

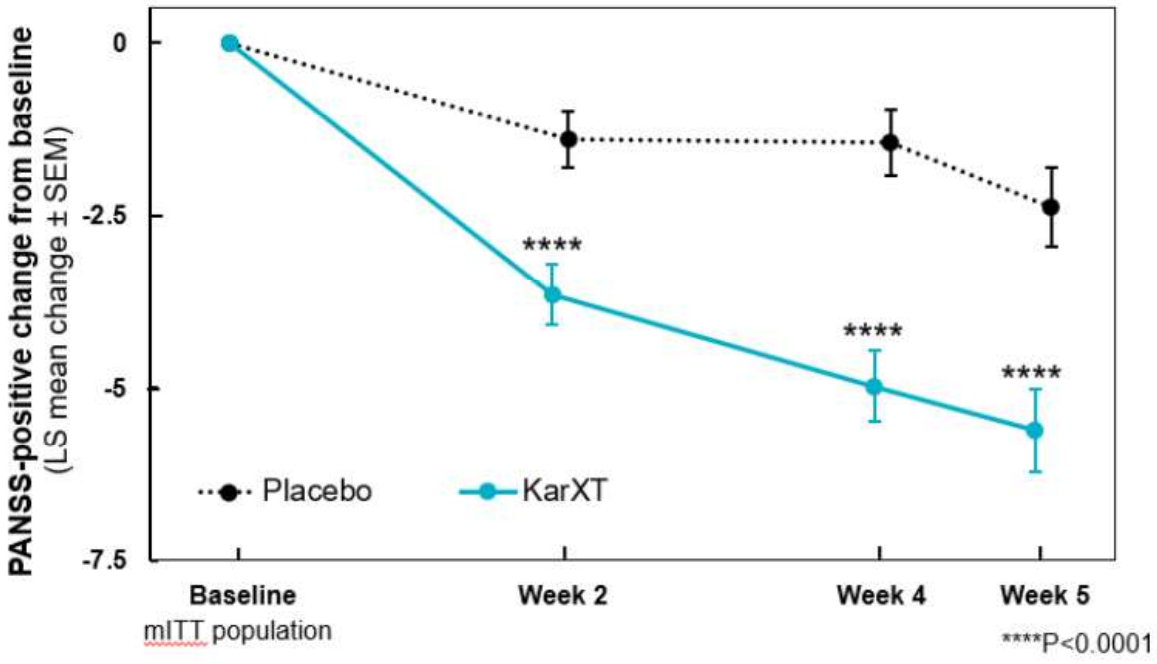
Figure 1. Change from Baseline in PANSS Total Scores (KAR-004)



Abbreviations: LS = least squares; mITT = modified intent-to-treat; PANSS = Positive and Negative Syndrome Scale; SEM = standard error of the mean.

A significant reduction in the secondary endpoint of PANSS-positive scores was observed ($p<0.0001$) at Week 5 as well as the 2 earlier time points (ie, Weeks 2 and 4; see Figure 2).

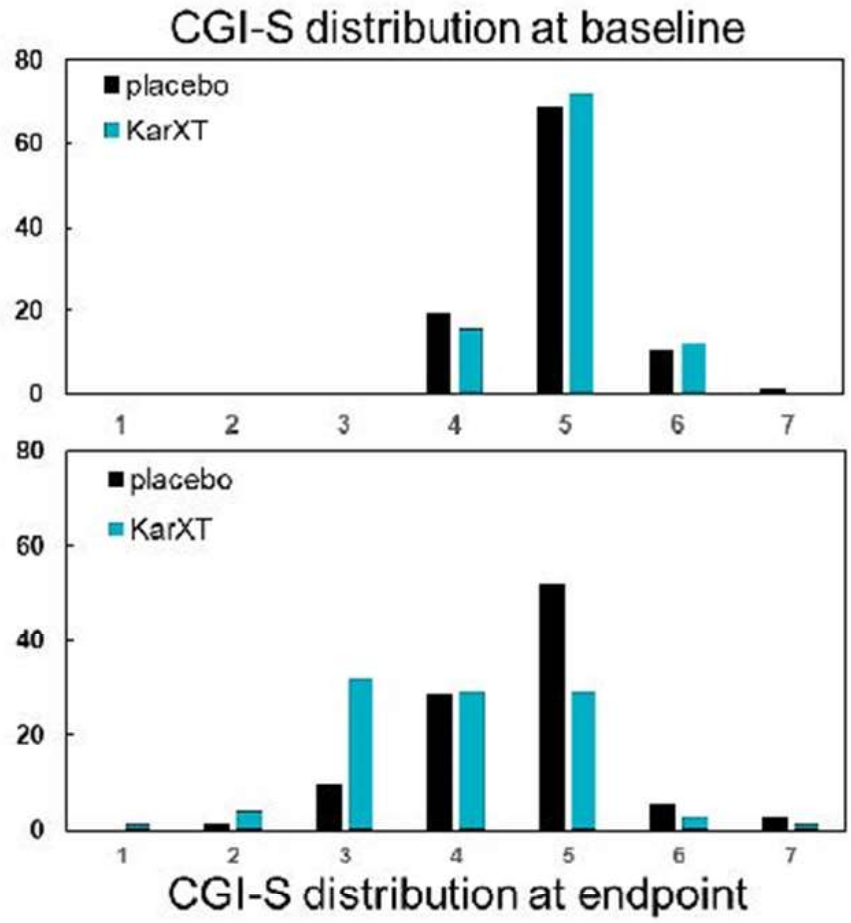
Figure 2. Change from Baseline in PANSS-Positive Scores (KAR-004)



Abbreviations: LS = least squares; mITT = modified intent-to-treat; PANSS = Positive and Negative Syndrome Scale; SEM = standard error of the mean.

As regards the Clinical Global Impression – Severity of Illness (CGI-S), subjects in the KarXT group overall significantly improved in ratings compared to placebo, with a p-value of <0.001 at Week 5. At Week 5, 8% of placebo subjects improved (decreased) their CGI-S ratings at least 2 levels versus 28.9% of KarXT subjects (see Figure 3).

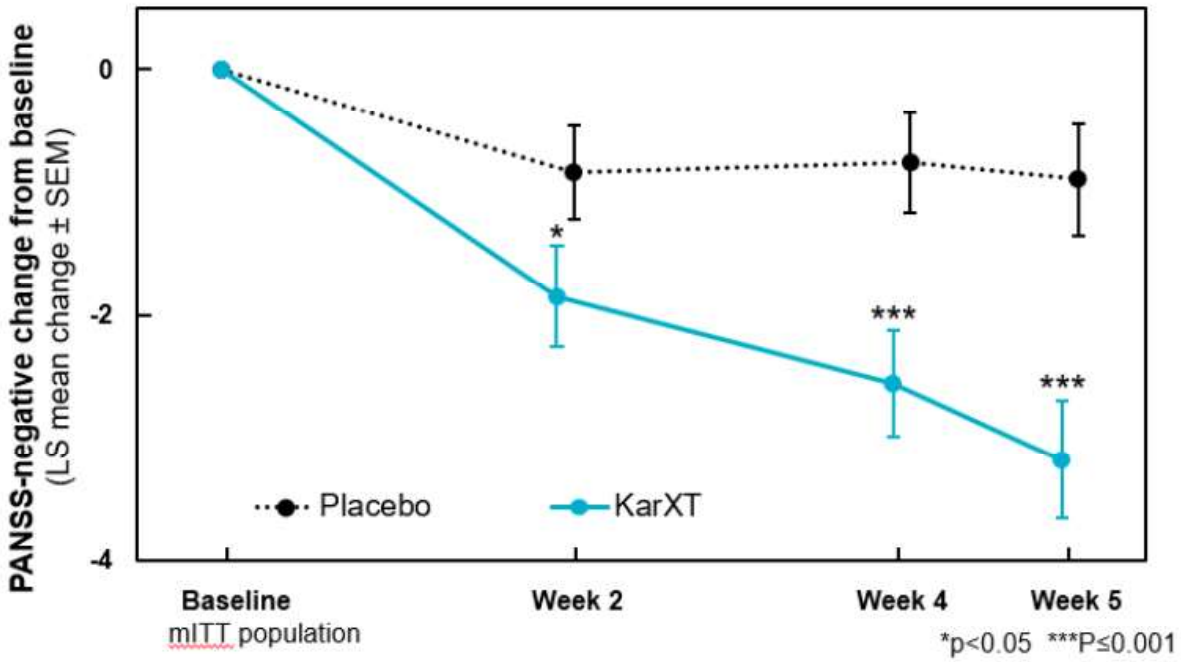
Figure 3. Change from Baseline in CGI-S (KAR-004)



Abbreviation: CGI-S = Clinical Global Impression–Severity.

A statistically significant reduction in the secondary endpoint of PANSS-negative score was observed (p<0.001) at Week 5. Overall, the changes in the KarXT group were statistically significantly greater compared to the placebo group at Visits 6, 8, and 9 (p<0.001). The least square mean improvement for the placebo group was 1.32 points at Week 5 (Visit 9) and the mean improvement for the KarXT group was 3.85 points leading to a mean difference of 2.53 points at Week 5 (Visit 9; see Figure 4).

Figure 4. Change from Baseline in PANSS-Negative Scores (KAR-004)



Abbreviations: LS = least squares; mITT = modified intent-to-treat; PANSS = Positive and Negative Syndrome Scale; SEM = standard error of the mean.

The overall safety/tolerability data were also fairly unambiguous; among the highlights:

- The overall discontinuation rate on KarXT was 20%, similar to placebo (21%). The number of discontinuations due to TEAEs was equal in the KarXT and placebo arms (N = 2 in each group)
- The dose escalation rate on KarXT was high and similar to placebo:
  - 91% of KarXT subjects escalated to 125/30 KarXT (vs 97% on placebo)
  - 4% percent de-escalated back to 100/20 KarXT dose (vs 1% on placebo)
- The overall TEAE rate on KarXT was 54% vs 43% on placebo:
  - The most common TEAEs were constipation, nausea, dry mouth, dyspepsia, and vomiting. None of these TEAEs were severe and none led to discontinuations
  - One SAE occurred in the study (the subject was on KarXT): the subject discontinued treatment and subsequently sought hospital care for worsening psychosis, meeting the regulatory definition of an SAE.
  - No syncope or mean changes in BP were seen

- A 5.5 bpm peak mean placebo adjusted resting heart rate increase with a downward trend after Week 2 was seen
- One subject (on KarXT) was discontinued due to an elevated gamma-glutamyl transpeptidase (GGT)
- There were no new safety findings associated with KarXT that have not been observed with either xanomeline alone or trospium alone in previous trials

- KarXT did not show evidence of many of the kinds of AEs that often occur in currently available antipsychotics for the treatment of schizophrenia
- The rates of the following AEs were similar for KarXT and placebo: somnolence, weight gain, and EPS

Two randomized, double-blind, placebo-controlled Phase 3 trials (KAR-007 and KAR-009) are planned in which the subjects will be exposed to either KarXT or placebo (1:1) for a period of up to 5 weeks. Subjects who complete either of these 2 studies will be eligible to roll over into this long-term open-label study.

5.3 Clinical Risks/Benefits of KarXT and Study Rationale

The risks and benefits of KarXT in humans are not fully known. KarXT is a fixed dose combination of xanomeline and trospium.

The available clinical trial data indicate that KarXT has robust efficacy and a favorable safety profile that appears unique compared to all available APDs. Most of these clinical data were generated by subjects who were either "institutionalized" or studied in an "inpatient" hospital setting. Treatment with KarXT is not associated with weight gain, sedation, or meaningful EPS changes. In contrast, these serious side-effects pose a significant risk with other APD treatments for schizophrenia and can lead to discontinuation of treatment and significant morbidity. A Phase 2 registration quality pivotal trial in 182 subjects met the primary endpoint with the PANSS total score showing a 11.6 point mean improvement compared to placebo with a highly significant ($p < 0.0001$) separation from placebo (-17.4 KarXT vs. -5.9 placebo) at Week 5. KarXT, as compared to placebo, demonstrated highly significant reduction in PANSS total scores ($p < 0.0001$) at all post randomization time points (Weeks 2, 4 and, 5) with a calculated effects size (Cohen's d) of 0.75. KarXT, as compared to placebo, demonstrated significant improvement at all post randomization time points for PANSS positive symptom subscores, PANSS negative symptom subscores, PANSS Marder Factor negative symptom subscores, and CGI-S scores.

Over 750 subjects or volunteers have been exposed to xanomeline tartrate (oral formulation; either alone, in combination with trospium, or as the combination drug KarXT) in clinical studies. These early clinical studies, as well as nonclinical pharmacology and toxicology studies, have not revealed any specific contraindications to the use of xanomeline. The most common side effects/symptoms are the cholinergic related effects: nausea, vomiting, excess salivation,

excess sweating, and diarrhea. In addition, subjects treated with xanomeline alone have reported both syncope and orthostatic dizziness. The addition of trospium decreases the peripheral cholinergic effect of xanomeline creating a better tolerated therapy. In addition, a titration phase also increases the tolerability of KarXT.

Trospium chloride has been marketed in the US for 12 years. The most frequently reported AEs reported in pivotal trials were dry mouth, constipation, abdominal pain, headache, urinary retention, and abnormal vision and accommodation. For additional information, the package insert for trospium chloride tablets for oral use can be found in the IB.

In a Phase 2 (KAR-004) clinical study, KarXT (100/20 and 125/30) significantly reduced the symptoms of schizophrenia in subjects with acute psychosis after treatment for 28 days. KarXT also showed an acceptable safety profile with the most common TEAEs being constipation, nausea, dry mouth, dyspepsia, and vomiting. All the reported TEAEs were mild or moderate in intensity. One SAE (psychotic disorder) was reported by a single subject and no deaths were reported in the study. KarXT was generally well-tolerated and found to be safe in this patient population.

KarXT represents a novel approach to the treatment of patients with schizophrenia that will provide an important and meaningful alternative to current therapies. The current tolerability and AE profile and the efficacy of KarXT justify further development of KarXT in this patient population by advancing to Phase 3 trials. Two such Phase 3 trials (KAR-007 and KAR-009) are planned where the subjects will receive the study drug (KarXT or placebo) for 5 weeks.

In the current study, regardless of treatment assignment in the preceding Phase 3 study (KAR-007 or KAR-009), all subjects will receive KarXT for a period of approximately 52 weeks with the primary objective of assessing the long-term safety and tolerability profile of KarXT in an out-patient setting. All subjects will start with a lead-in dose of KarXT 50/20 BID for Days 1 to 2 and then the dose will be titrated to 100/20 BID for Days 3 to 7, allowing the subject to adjust to KarXT before receiving a higher dose of 125/30 BID starting on Day 8, unless the subject is continuing to experience AEs from the previous dose increase of KarXT 100/20 BID. All subjects who are increased to KarXT 125/30 BID, depending on tolerability, will have the option to return to KarXT 100/20 BID for the remainder of the treatment period. Re-escalation to 125/30 BID or re-titration in cases where subject has been off the KarXT for a longer period of time is allowed and will require a discussion between the principal investigator (PI) and the medical monitor.

Dosing will occur every 12 ±4.5 hours each day, during waking hours. KarXT should be dosed on an empty stomach: ie, at least 1 hour before a meal or 2 to 3 hours after a meal.

The current study is designed to demonstrate that long-term treatment with KarXT in adult schizophrenia subjects is safe and tolerable.

6 STUDY OBJECTIVES AND ENDPOINTS

6.1 Study Objectives

6.1.1 Primary Objective

The primary objective of the study is to assess the long-term safety and tolerability of KarXT in subjects with a DSM-5 diagnosis of schizophrenia.

6.1.2 Secondary Objective

The secondary objective of this study is to assess the long-term efficacy and monitor trough concentrations of xanomeline and trospium after administration of KarXT in adults with a DSM-5 diagnosis of schizophrenia:

- To evaluate the reduction in PANSS total score
- To evaluate the reduction of PANSS positive score
- To evaluate the improvement in Clinical Global Impression Severity (CGI-S) results
- To evaluate the reduction of PANSS negative score
- To evaluate the reduction of PANSS Marder Factor negative symptoms score
- To measure trough concentrations of xanomeline and trospium after administration of KarXT in adults who are acutely psychotic with a DSM-5 diagnosis of schizophrenia

6.1.3 Exploratory Objective

The exploratory objectives of this study are:

- To evaluate cognition with the Cambridge Neuropsychological Test Automated Battery (CANTAB)
- To evaluate prolactin levels after administration of KarXT
- To evaluate digital biomarkers of schizophrenia
- To evaluate Ecological momentary assessment (EMA) in schizophrenia
- To evaluate cognitive insight

6.2 Study Endpoints

6.2.1 Primary Safety Endpoint

The primary safety endpoint of this study is the incidence of treatment-emergent AEs (TEAE).

6.2.2 Secondary Endpoints

6.2.2.1 Safety Endpoints

The secondary safety endpoints of this study are:

- Incidence of serious TEAEs

- Incidence of TEAEs leading to withdrawal

6.2.2.2 Efficacy Endpoints

The secondary efficacy endpoints of this study are:

- Change from baseline in PANSS total score at Week 52
- Change from baseline in PANSS positive score at Week 52
- Change from baseline in PANSS negative score at Week 52
- Change from baseline in PANSS Negative Marder Factor score at Week 52
- Change from baseline in CGI-S score at Week 52
- Percentage of PANSS responders (a 30% change in PANSS total score) at Week 52

6.2.3 Other Endpoints

6.2.3.1 Safety Endpoints

- Spontaneously reported cholinergic symptoms
- Change from baseline in Simpson-Angus Rating Scale (SAS)
- Change from baseline in Barnes Rating Scale for Akathisia (BARS)
- Change from baseline in Abnormal Involuntary Movement Scale (AIMS)
- Change from baseline in body weight, body mass index (BMI), waist circumference
- Change from baseline in orthostatic vital signs (supine and standing after 2 minutes): BP (systolic and diastolic) and heart rate
- Change from baseline in clinical laboratory assessments (hematology, clinical chemistry, coagulation, urinalysis, and drug screen)
- Change from baseline in 12-lead ECG
- Change from baseline in physical examination
- Suicidal ideation scale with the use of Columbia-Suicide Severity Rating Scale (C-SSRS)

6.2.3.2 Pharmacokinetic Endpoint

The PK endpoint of this study is to measurement of trough plasma concentrations of xanomeline and trospium.

6.2.4 Exploratory Endpoints

The exploratory endpoints of this study are:

- Change from baseline in cognition measuring core domains of impairment in schizophrenia using CANTAB
- Change from baseline in prolactin levels
- Observed digital biomarkers of schizophrenia
- Observed EMA data over time in schizophrenia
- Observed cognitive insight data over time

7 INVESTIGATIONAL PLAN

7.1 Description of Overall Study Design and Plan

This is a Phase 3 multicenter, 53-week, outpatient, open-label extension (OLE) study to evaluate the long-term safety, tolerability, and efficacy of KarXT in subjects with DSM-5 schizophrenia who previously completed the treatment period of one of the two Phase 3 double-blind studies, KAR-007 or KAR-009. The study consists of a 52-week OLE treatment phase and a 7-day (±3 days) follow-up/end-of-study (EOS) visit after the last KarXT dose for subjects who complete the treatment phase and those who prematurely discontinue from the study.

After written informed consent, subjects who have completed either the KAR-007 or KAR-009 Phase 3 acute study and received the last dose of the study drug in that trial will be rolled over in to the current OLE study. The assessments performed on Day 35 of Studies KAR-007 or KAR-009 will be considered as baseline assessments along with any additional assessments that will be performed on Day 1 of the current study. Consenting subjects who roll over into KAR-008 will be dosed with a lead-in dose of open-label KarXT the next day after completion of Visit 10 (Day 35) from the prior Studies KAR-007 or KAR-009. The rollover is designed as above; a window extension is permitted but will need discussion with, and approval by, the medical monitor.

Subjects who did not complete the full treatment period, or who early terminated Studies KAR-007 or KAR-009, will not be eligible to enroll in this long-term extension study.

A total of up to 350 subjects are planned to be enrolled in this study (aged 18 to 65 years) across approximately 30 study sites in the United States and 10 study sites in Ukraine.

In this OLE study, all subjects will receive KarXT for up to 52 weeks. Regardless of treatment assignment in the preceding Phase 3 acute study (KAR-007 or KAR-009), all subjects will start on a lead-in dose of KarXT 50/20 BID for the first 2 days (Days 1 and 2), followed by KarXT 100/20 BID for the remainder of Week 1 (Days 3 to 7). On Day 8, dosing will be titrated upwards to KarXT 125/30 BID unless the subject is continuing to experience AEs from the previous dose of KarXT 100/20 BID. All subjects who are increased to KarXT 125/30 BID, depending on tolerability, will have the option to return to KarXT 100/20 BID for the remainder of the treatment period. Re-escalation to 125/30 BID or re-titration in cases in which the subject has been off KarXT for a longer period of time (at least a week) is allowed and will require a discussion between the PI and the medical monitor. Additional changes to KarXT dosing (e.g., temporary dose reductions) may be permitted as clinically indicated upon approval by the medical monitor.

Beginning after Visit 5/Day 28, interim visits will be completed with flexibility between the in-clinic visits, approximately once every 4 weeks For interim visits, either a Home Health Care

nurse or the study site staff will visit the subject to complete the scheduled visit. In addition to augment at-home visits, the telemedicine visit can be used. When needed, the sites will have the option to schedule a subject for an in-clinic visit.

All subjects will have structured diagnostic interview sessions and questionnaires administered throughout the study (see Schedule of Assessments Table 2). Analyses of change from baseline in diagnostic measures will be performed.

Safety will be assessed through spontaneous AEs; SAEs and AEs leading to discontinuation of KarXT; cholinergic symptoms; SAS; BARS; AIMS; body weight; BMI; waist circumference; orthostatic vital signs; clinical laboratory assessments (hematology, clinical chemistry, coagulation, urinalysis, and drug screen), 12-lead ECG; physical examination; and C-SSRS will be evaluated throughout the study as scheduled. Section 11 provides complete details on these safety assessments.

Efficacy will be assessed through PANSS total score, PANSS-positive score, PANSS-negative score, PANSS Negative Marder Factor score, and CGI-S score at scheduled visits. Refer to Section 12 for more details.

Details on PK assessments are provided in Section 13 and include monitoring of trough concentrations at scheduled visits.

Exploratory assessments include cognition testing using CANTAB; digital biomarkers of schizophrenia; EMA; and cognitive insight, which will be evaluated at scheduled visits. See Section 14 for more details.

A safety follow-up/end of study/ET visit (Visit 30/Day 371 ±3 days) will be performed for all subjects after the last dose of KarXT.

An Independent Safety Monitoring Committee (ISMC) will be responsible for periodically reviewing the safety data from this study and confirming that the study may continue.

Table 1 presents the study design.

Table 1 Study Design

Period:	Open-Label Extension Treatment[a]							End of Treatment	EOS/ET/UNS
Day:	Day 1	Day 3 +1 day	Day 8 ±1 day	Day 14 ±2 days	Day 28[b] ±3 days	Day 56 ±3 days	Days 84 to 350 ±3 days	Day 364 ±3 days	Day 371 ±3 days
Visit:	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5[b]	Visit 7	Visits 9 to 28	Visit 29	Visit 30
Xanomeline/ trospium (KarXT)*:	50/20 BID	100/20 BID	125/30 BID (Option: 100/20 BID)[c]	125/30 BID (Option: 100/20 BID)[c,d]	125/30 BID (Option: 100/20 BID)[c,d]	125/30 BID (Option: 100/20 BID)[c,d]	125/30 BID (Option: 100/20 BID)[c,d]	125/30 BID (Option: 100/20 BID)[c,d]	N/A
Comment(s):	2-day lead-in dose	Upward titration of dose	Upward titration of dose						7 (±3) days after the last dose or for ET from the study or UNS

Abbreviations: BID = twice daily; EOS = end of study; ET = early termination; N/A = not applicable; PI = principal investigator; UNS = unscheduled.
* All the KarXT doses are in mg.

a. Visits 1, 2, 3, 4, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, and 30 are in-clinic/on-site visits. Visits 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28 are interim visits.
b. Beginning after Visit 5/Day 28, interim visits will be completed with flexibility between in-clinic visits, approximately once every 4 weeks.
c. All subjects who are increased to KarXT 125/30, depending on tolerability, will have the option to return to KarXT 100/20 BID for the remainder of the treatment period.
d. Re-escalation to 125/30 BID or re-titration in cases where subject has been off KarXT for a longer period of time (at least a week) is allowed and will require a discussion between the PI and the medical monitor. Additional changes to KarXT dosing (e.g., temporary dose reductions) may be permitted as clinically indicated upon approval by the medical monitor.

7.2 Discussion of Study Design

The KarXT clinical development program includes this open-label extension study to evaluate the long-term safety, tolerability, and efficacy data for KarXT in subjects with schizophrenia who participated in either of the 2 Phase 3 double-blind clinical studies and completed the treatment period without any tolerability/safety issues.

This study will allow subjects that were randomized into a preceding Phase 3 study (KAR-007 or KAR-009) to reinstitute (or initiate treatment if a placebo subject) KarXT therapy. Subjects will receive KarXT (with the same lead-in dose of KarXT 50/20 BID), regardless of treatment assignment from the preceding Phase 3 study. Thus, subjects who received placebo during the preceding Phase 3 study who may not have demonstrated clinical benefit, nonetheless, may be considered appropriate for the current study, as all subjects will receive KarXT.

The dosing plan for this study has been established and follows the earlier studies. All eligible subjects will receive the same lead-in doses of KarXT (KarXT 50/20 BID). Dosing will be titrated to 100/20 BID on Day 3 and further titrated to 125/30 BID on Day 8, unless the subject continues to experience AE(s) from the previous dose increase of KarXT.

During the study, all subjects who are increased to the highest dose of KarXT, depending on tolerability, will have the option to return to the next lower dose of KarXT (100/20 BID) for the remainder of the treatment period. Re-escalation to 125/30 BID or re-titration in cases where subject has been off KarXT for a longer period of time (at least a week) is allowed and will require a discussion between the PI and the medical monitor.

Beginning after Visit 5/Day 28 (approximately 1 month of KarXT treatment), interim visits will be completed every 4 weeks between the in-clinic visits, to allow for subject safety monitoring and IP dispensing and accountability. For interim visits, either a Home Health Care nurse or the study site staff will visit the subject to complete the scheduled visit. In addition to augment at-home visits, the telemedicine visit can be used. When needed, the sites will have the option to schedule a subject for an in-clinic visit.

A 52-week treatment phase is considered to be sufficient to demonstrate the long-term safety and tolerability of KarXT. A sample size of approximately 350 subjects is also determined to be an appropriate number of evaluable subjects to assess the long-term safety of KarXT administration. Section 5.2 details the nonclinical and clinical background information available on KarXT, including dose rationale.

7.3 End of Study

A subject will have fulfilled the requirements for study completion if/when the subject has completed the study treatment, including the EOS visit or the last scheduled visit as indicated in the Schedule of Assessments (Table 2) in accordance with the protocol.

7.4 Independent Safety Monitoring Committee

For the purpose of this study, the ISMC is an independent group of individuals with pertinent expertise that reviews on a regular basis accumulating safety data from the clinical study. This committee will be responsible, on a periodic basis, for confirming the safety of KarXT throughout the study, with particular focus on assessing for any new or long-term toxicities that might be involved with KarXT.

The reviews will allow a comparison of event rates and detection of safety signals, and to identify important safety information. The ISMC charter will contain the details of the types of data to be reviewed, the defined triggers for review, the minimum frequency of meetings (timed, if no triggers), and the communication plan for disseminating review recommendations.

8 SELECTION OF STUDY POPULATION

Section 7.1 provides information regarding the number of subjects planned to be enrolled.

8.1 Inclusion Criteria

Individuals must meet all of the following criteria to be included in the study:

1. Subject is aged 18 to 65 years, inclusive. Exception: Subjects who turned 66 during KAR-007/009 participation will be eligible to continue in KAR-008.
2. Subject is capable of providing informed consent.
    a. A signed informed consent form must be provided before any study assessments are performed.
    b. Subject must be fluent in (oral and written) English (United States only) or local language (Ukraine only) to consent.
3. Subject has completed the treatment period on study drug (through Day 35 -2 days) of Studies KAR-007 or KAR-009.
4. Subject resides in a stable living situation, in the opinion of the investigator.
5. Subject has an identified, reliable informant/caregiver. An informant/caregiver is needed at the baseline visit as well as at the end of the study for relevant assessments. An informant/caregiver may not be necessary if the subject has been the patient of the investigator for ≥1 year.
6. Women of childbearing potential (WOCBP) or men whose sexual partners are WOCBP must be sexually abstinent (in line with their preferred and usual lifestyle) or willing and able to use at least 1 highly effective method of contraception during the study and for at least 7 days after the last dose of KarXT. Sperm donation is not allowed for 90 days after the final dose of KarXT. A female subject is considered to be a WOCBP after menarche and until she is in a postmenopausal state for 12 consecutive months or is otherwise permanently sterile (for which acceptable methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy) [22]. For the definition and list of highly effective methods of contraception, see APPENDIX 1.

8.2 Exclusion Criteria

Subjects will be excluded from the study if 1 or more of the following criteria is/are applicable:

1. Risk for suicidal behavior during the study as determined by the investigator's clinical assessment and C-SSRS as confirmed by the following:
    a. Subject answers "Yes" to "suicidal ideation" Item 4 (active suicidal ideation with some intent to act, without specific plan) or Item 5 (active suicidal ideation with specific plan and intent) on the C-SSRS assessment.
    b. Nonsuicidal self-injurious behavior is not exclusionary.
2. Any clinically significant abnormality including any finding(s) from the physical examination, vital signs, ECG, or laboratory test at the end-of-treatment visit of Studies

KAR-007 or KAR-009 that the investigator, in consultation with the medical monitor, would consider to jeopardize the safety of the subject.

3. Female subject is pregnant.
4. If, in the opinion of the investigator (and/or Sponsor), subject is unsuitable for enrollment in the study or subject has any finding that, in the view of the investigator (and/or Sponsor), may compromise the safety of the subject or affect his/her ability to adhere to the protocol visit schedule or fulfill visit requirements.
5. Subjects with extreme concerns relating to global pandemics such as coronavirus disease 2019 (COVID-19) that preclude study participation.
6. Risk of violent or destructive behavior.
7. Subjects participating in another investigational drug or device trial or planning on participating in another clinical trial during the course of the study.

8.3 Retesting for Eligibility

Subjects who are willing to participate in the study but who do not meet all the requirements for safety laboratory assessments performed on Day 35 -2 days of Studies KAR-007 or KAR-009 and therefore do not enroll, may be retested (retesting for elevated LFTs is not allowed) upon approval of the medical monitor on a case-by-case basis. However, these subjects will be dosed on Day 1 and will be retested as needed upon availability of the laboratory test results. Any abnormal lab values deemed to be clinically significant by the PI should be reported as AEs and dosing changes made as appropriate. Such subjects may be allowed to be retested up to 1 time. When re-testing within the same end of treatment procedure of Studies KAR-007 or KAR-009, only the exclusionary laboratory tests will be repeated once, in case the exclusionary laboratory result is not due to a pathological condition and is occasional.

8.4 Study Withdrawal, Removal, and Replacement of Subjects

If a subject discontinues study treatment and is withdrawn from the study for any reason, the study site must immediately notify the medical monitor. The date and the reason for study discontinuation must be recorded on the electronic case report form (eCRF). Subjects who complete or discontinue early from the study will be asked to return to the study site within 7 (±3) days of the last administration of KarXT to complete EOS assessments as indicated in the Schedule of Assessments (Table 2).

In the event that a subject discontinues prematurely from the study because of a treatment-emergent AE (TEAE) or serious TEAE, the TEAE or serious TEAE will be followed up until it resolves (returns to normal or baseline values) or stabilizes, or until it is judged by the investigator to no longer be clinically significant.

Once a subject is withdrawn from the study, the subject may not re-enter the study.

A subject may voluntarily withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following:

- progressive disease
- unacceptable toxicity or AE
- subject withdrawal of consent: at any time, a subject's participation in the study may be terminated at his/her request or on the basis of the investigator's clinical judgment; the reason for subject withdrawal will be noted on the eCRF
- intercurrent illness: a condition, injury, or disease unrelated to the primary diagnosis that became apparent during treatment and necessitated the subject's termination from the study
- general or specific changes in the subject's condition that renders him/her ineligible for further treatment according to the inclusion/exclusion criteria (eg, subject has need for a medication prohibited by the protocol)
- subject fails to adhere to the protocol requirements (eg, drug noncompliance [if a subject is off KarXT for >5 consecutive days])
- violation of entry criteria, ie, enrolled subjects who are later discovered not to meet eligibility criteria
- development of suicidal or assaultive behavior
- alcohol or illegal drug use
- pregnancy, as indicated in Section 11.7.7. Any female study subject or female partner of the male subject becomes pregnant while participating in the study and is willing and able to consent to pregnancy follow-up, will be followed until her pregnancy reaches term.
- Sponsor's decision to discontinue study

Subjects who withdraw from the study will be encouraged to complete the same final evaluations as subjects completing the study according to this protocol, particularly safety evaluations. The aim is to record data in the same way as for subjects who completed the study.

Reasonable efforts will be made to contact subjects who are lost to follow-up. A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study center. These efforts must be documented in the subject's file. Subjects with AEs ongoing at end of study will be followed until the AE is resolved or the subject is considered to be in stable condition.

The Sponsor has the right to terminate the study at any time in case of SAEs or if special circumstances concerning the KarXT become known, making further treatment of subjects impossible. In this event, the investigator(s) will be informed of the reason for study termination.

8.4.1 Pregnancy

No evidence of mutagenicity, or treatment effects on reproduction, fertility, or fetal parameters have been demonstrated in animals following administration of xanomeline, but there are no adequate and well-controlled studies in pregnant women (FDA Pregnancy Category B). Animal reproduction studies of trospium chloride have shown an adverse effect on the fetus, but potential benefits may warrant the use of the drug in pregnant women despite the risk (FDA Pregnancy Category C).

Therefore, WOCBP in this study must be willing to use a highly effective method of birth control (see APPENDIX 1 for a list of acceptable highly effective methods of contraception) during the study and for 7 days after the last dose of KarXT. WOCBP will have a urine pregnancy test on Day 1 (before receiving KarXT) and thereafter, as designated at other scheduled visits (Table 2). In case of positive urine pregnancy test result, a serum pregnancy test should be performed to confirm the result.

Pregnant women are excluded from this study because the effects of KarXT on the developing human fetus are unknown with the potential for teratogenic or abortifacient effects.

Because there is an unknown but potential risk for AEs in nursing infants secondary to treatment of the mother with KarXT, women who become pregnant must discontinue KarXT immediately.

The effects of KarXT on sperm are unknown. Male subjects whose sexual partners are WOCBP must agree to use a highly effective method of birth control (see APPENDIX 1 for a list of acceptable highly effective methods of contraception) and must not impregnate a sexual partner during or for 90 days after the last dose of KarXT. They must also agree to refrain from sperm donation for 90 days after the last dose of KarXT.

WOCBP will be instructed that known or suspected pregnancy occurring during the study should be confirmed and reported to the investigator. If a female subject becomes pregnant, the investigator must withdraw her from the study without delay. The subject must not receive any further doses of the KarXT. The investigator must notify the Sponsor or the designee of any female subject or female partner of a male subject that becomes pregnant while participating in the study. If the female subject or the female partner of the male subject is willing and able to consent to pregnancy follow-up, she will be followed until her pregnancy reaches term. Only those procedures that would not expose the pregnant female patient to undue risk will be performed. See Section 11.7.7 for further reporting and monitoring details.

Full details of the pregnancy will be recorded on the withdrawal page (exit form) of the eCRF, or a Pregnancy Reporting Form will be completed if the subject has completed the study. Notification of the pregnancy should be submitted via the Pregnancy Reporting Form within 24 hours of knowledge of the pregnancy. Pregnancy is not to be considered an AE; however, it must be reported using the same procedure as described for reporting SAEs, Section 11.7.4.

8.5 Completion of the Study or Lost to Follow-up

The study will be completed when all subjects have completed their study-related procedures in accordance with the protocol.

Every reasonable effort will be made to contact subjects who are lost to follow-up to obtain EOS information. Details regarding follow-up efforts are to be documented in the subject's medical records/source documentation.

8.6 Study Termination

The availability of any new adverse safety information related to KarXT may result in stopping the study. An investigator, Sponsor, or Institutional Ethics Committee (IEC)/Institutional Review Board (IRB) may take such actions. If the study is terminated for safety reasons, subjects will be notified immediately and assured that appropriate treatment and follow-up will be available. If an investigator terminates the study, the Sponsor, subjects, and IEC/IRB will be informed about the reason for such action. Similarly, if the Sponsor terminates the study, it will inform the investigators, the IEC/IRB, and the subjects of the reason for such an action. Similar notifications will be sent by the IEC/IRB if it takes such an action.

9 TREATMENTS

9.1 Details of Study Treatments

KarXT is formulated as hard hydroxypropyl methylcellulose oral capsules containing 2 distinct populations of drug beads, 1 of which is loaded with xanomeline tartrate and the other of which is loaded with trospium chloride. Each capsule contains the free base equivalent of xanomeline and trospium according to the desired dosage strength. In addition to the active ingredients, the drug beads contain microcrystalline cellulose (MCC). The beads are not coated and are formulated for immediate release of the active ingredients.

9.1.1 Identity of Study Treatments

Active study agents for treatment group will be size 0, Swedish orange, opaque, and hydroxypropyl methylcellulose hard capsules. For the 2-day lead-in period (Days 1 and 2), subjects will receive capsule strength KarXT 50/20 BID, followed by 2 capsules of KarXT 50/10 mg BID or a dosage of 100/20 mg BID for a total daily dose of 200/40 mg for the remainder of Week 1 (Days 3 to 7). At the beginning of Week 2, dosing may be increased to 2 capsules of KarXT 62.5/15 mg or a dosage of 125/30 mg BID for a total daily dose of 250/60 mg, depending on tolerability. Investigators have the option to return a subject to KarXT 100/20 mg BID for the remainder of the treatment period. Re-escalation to 125/30 BID or re-titration in cases where subject has been off KarXT for a longer period of time (at least a week) is allowed and will require a discussion between the PI and the medical monitor.

Note: In these cases of dose reduction, re-escalation or re-titration, additional PK samples will be collected at 8 and 14 days post dose reduction, re-escalation, or re-titration in accordance with the Visits 3 and 4 schedules, respectively, and the original PK sampling schedule will be followed thereafter.

KarXT 50/10 mg is composed of 44.4% xanomeline tartrate, 5.8% trospium chloride, excipients 37.59% MCC, 11.5% lactose monohydrate, 0.3% ascorbic acid and 0.5% talc in a size 0, Swedish orange, hydroxypropyl methylcellulose hard capsule.

KarXT 50/20 mg is composed of 33.4% xanomeline tartrate, 8.7% trospium chloride, excipients 39.8% MCC, 17.3% lactose monohydrate, 0.3% ascorbic acid and 0.5% talc in a size 0, Swedish orange, hydroxypropyl methylcellulose hard capsule.

KarXT 62.5/15 mg is composed of 41.7% xanomeline tartrate, 6.5% trospium chloride, excipients 38.1% MCC, 12.9% lactose monohydrate, 0.3% ascorbic acid and 0.5% talc in a size 0, Swedish orange, hydroxypropyl methylcellulose hard capsule.

All investigational agents are to be stored according to requirements.

9.1.2 Packaging and Labeling

The study packaging and labeling will be performed by Corealis Pharma, located in Laval, Quebec, Canada and Catalent Pharma Solutions, located in Winchester, Kentucky (labelling for the US sites), and Catalent Pharma Solutions, located in Philadelphia, Pennsylvania (labelling for Ukrainian sites). All packaging and labeling operations will be performed according to Good Manufacturing Practice for Medicinal Products and the relevant regulatory requirements.

Bulk supply bottles are labeled with the name of the drug, recommended storage conditions, the name and address of the manufacturer and the Investigational Use Statement (for the US sites: "Caution: New Drug – Limited by Federal [USA] Law to Investigational Use" and for the Ukrainian sites: "For clinical trial use only" or similar wording).

Further details on labeling of investigational product will be provided in the Pharmacy Manual.

Subjects will be provided an automated medication dispenser which will be prefilled with medication at scheduled intervals. Full details on study medication dispensing can be found in the Pharmacy Manual.

9.1.3 KarXT Storage

Prior to dispensing KarXT to the subjects, it must be stored at controlled room temperature 15˚C-25˚C.

9.1.4 KarXT Retention

KarXT must be retained until completion or termination of the study, and written authorization from the Sponsor has been received. All unused and used KarXT must be destroyed at the site or returned, as specified by Sponsor. It is the investigator's responsibility to ensure that the Sponsor has provided written authorization prior to return or destruction, and that appropriate records of the disposal are documented and maintained. No used or unused KarXT may be disposed until fully accounted for by the study monitor.

9.2 Dosage Schedule

Subjects who roll over into KAR-008 will be dosed on the next day after completion of Visit 10 (Day 35) in Study KAR-007 or KAR-009. The first dose of the KarXT will be administered in the morning of Day 1 and the last dose will be administered in the evening of Day 364 (±3 days). KarXT should be administered daily BID on an empty stomach (ie, at least 1 hour before a meal) or 2 to 3 hours after a meal. Some considerations for dosing and PK blood withdrawals are provided in the subsections below.

9.2.1 Visit 1/Day 1 Dosing

- The first dose will be administered in the morning and the evening dose will be administered at 12 (±4.5) hours after the morning dose.

- All subjects must be administered 4 doses of the KarXT 50/20 before dose escalation to KarXT 100/20 BID.

9.2.2 Visit 2/Day 3 and/or Other Visits Occurring on Weekends/Holidays

- When Day 3 occurs on a weekend, it is expected that the complete Visit 2 will be performed, and the subject's dose will be escalated on Day 3.
- If completion of the visit is not possible on Day 3, the +1-day visit window may be used. In this instance, the dose will not be up-titrated until the study visit occurs. In all cases, the subject must have had at least 4 doses of KarXT 50/20 before escalating to KarXT 100/20.
- This may result in only 4 days of the KarXT 100/20 dose at Visit 3/Day 8, which is acceptable.
- All the subjects must be administered 8 doses of the KarXT 100/20 before dose escalation to KarXT 125/30 BID.

9.2.3 Visit 3/Day 8 and Visit 4/Day 14 Dosing and PK considerations

- If dose escalation to the KarXT 125/30 level is confirmed by investigator order on Visit 3/Day 8, that dose is to be administered in the morning (after the pre-dose PK blood draw) (Table 2).
- If the use of visit windows becomes necessary, PK sampling **must** accompany the actual day of uptitration for Visit 3/Day 8.
- On Days 8 and 14, 3 PK samples will be collected at pre-dose in the morning, 1 hour (±5 min), and 2 hours (±10 min) postdose.

Note: In case of dose reduction, re-escalation, or re-titration, additional PK samples will be collected at 8 and 14 days post dose reduction, re-escalation, or re-titration in accordance with the Visits 3 and 4 schedules, respectively, and the original PK sampling schedule will be followed thereafter.

9.3 Measures to Minimize Bias: Study Treatment Assignment

9.3.1 Method of Study Treatment Assignment

The 9-digit Subject Number previously assigned to the subject in the Study KAR-007/KAR-009 will continue to be used in the current Study KAR-008. This number will be associated with the subject throughout the current study.

9.3.2 Blinding

This is an open-label study; therefore, blinding is not applicable.

9.4 Dosage Modification

Subjects will self-administer the KarXT as described in Section 7.1 and in accordance with the Schedule of Assessments (Table 2). The KarXT doses were selected based on the previous preclinical and clinical studies (see Section 5.2). Per the protocol, subjects will be evaluated for dose adjustments starting at Visit 3 through the remainder of the treatment period (see Section 9.1.1).

9.5 Treatment Accountability and Compliance

The pharmacist or other designated individual will maintain records of study treatment delivered to the study site, the inventory at the study site, the distribution to each subject, and the return of materials to the Sponsor or designee for storage or disposal. These records should include dates, quantities, batch/serial numbers, expiration dates, temperature log, and unique code numbers assigned to the product and study subjects.

Administration of KarXT will be supervised by study site personnel (during in-clinic visits) and by a digital compliance tool to ensure compliance (AiCure technology). Also, KarXT will be dispensed using MedReady time-controlled dispensing device, which dispenses KarXT at scheduled intervals. Subjects will be advised to return the MedReady device to the site staff at each in-clinic visit for drug accountability and refilling.

For interim visits, the empty or unused dosettes will be collected by the Home Health Care nurse and/or site staff. In case a Home Health Care nurse performs the interim visit, he/she will perform a preliminary drug accountability before shipping the empty or unused dosettes to the study site for final accountability check. Full details can be found in the Pharmacy Manual.

Investigators will maintain records that adequately document that the subjects were provided with the correct study treatment supply and reconcile the usage of the study drug. Investigational product will not be returned to the Sponsor or designee until accountability has been fully monitored through the end of the study. KarXT accountability will be assessed periodically by the assigned study monitor.

9.6 Prior and Concomitant Therapy

9.6.1 Prior and Concomitant Medications

Subjects will be asked to confirm all prior medications taken up to 6 months before the current study (and recorded from the lead-in study), up to the time of the first dose of study medication on Day 1. All prior medications will be recorded on the eCRF.

Restricted prior therapies are provided below.

All medications and other treatments taken by the subject during the study, including those treatments initiated before the start of the study, must be recorded on the eCRF.

During the study (ie, from the time of enrollment at baseline visit [Day 1] until study completion [EOS/ET]), subjects will refrain from the use of any new concomitant medications without the specific prior approval of the investigator. The administration of any other concomitant medications during the study period is prohibited without the prior approval of the investigator unless its use is deemed necessary in a medical emergency. Any medication or therapy that is taken by or administered to the subject during the course of the study must be recorded in the eCRF. The entry must include the dose, regimen, route, indication, and dates of use.

All the subjects enrolled in to the study must not take the below mentioned prohibited medications for the duration of the study.

- Oral antipsychotic medications, monoamine oxidase inhibitors, mood stabilizers (ie, lithium), anticonvulsants (eg, lamotrigine, Depakote), tricyclic antidepressants (eg, imipramine, desipramine), selective serotonin reuptake inhibitors, or any other psychoactive medications except for anxiolytics that were taken on an as needed basis (eg, lorazepam, chloral hydrate).
- Long acting injectable antipsychotics (including INVEGA TRINZA®).

Note: Please direct questions relating to prohibited medications to the medical monitor.

9.6.2 Concomitant Medications for Anxiety and/or Sleep Aid

Subjects are allowed to take benzodiazepines (up to 6 mg lorazepam/day or equivalent) for anxiety, agitation, and insomnia. Subjects may also use non-benzodiazepine medications (eg, zolpidem, zaleplon) as a sleep aid. Study sites must record the use of concomitant medications in the eCRF and subject's source document. Note: Cognition testing should not be done within 8 hours of receiving a benzodiazepine or sleep medication.

10 STUDY PROCEDURES

Table 2 outlines the timing of procedures and assessments to be performed throughout the study. Section 11.6 specifies laboratory assessment samples to be obtained. See Sections 11, 12, 13, and 14 for additional details regarding efficacy, safety, PK, and exploratory assessments, respectively.

See APPENDIX 3 for alterative procedures during COVID-19 pandemic-related physical distancing.

If a subject tests positive for COVID-19 during the study, he/she may be quarantined as needed and any scheduled visits should be rescheduled or alternative procedures (see APPENDIX 3) be followed at the discretion of the investigator. If the subject requires hospitalization, an SAE should be reported and the subject should be followed up as outlined in Section 11.7.4.

Table 2. Schedule of Assessments

DAY (± 3d, unless otherwise noted)	1	3 (+1d)	8 (± 1d)	14 (± 2d)	28	42	56	70	84	98	102	116	130	154	168
WEEK	1			2	4[a]	6	8	10	12	14	16	18	20	22	24
VISIT	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
TYPE OF VISIT	Clinic	Clinic	Clinic	Clinic	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic
PROCEDURE															
Written informed consent	X														
Subject eligibility verification	X														
Urine pregnancy test (WOCBP only)[b]	X		X		X		X		X		X		X		X
Urine drugs of abuse and alcohol testing[c]	X	X	X	X	X		X		X		X		X		X
Review of inclusion/exclusion criteria	X														
Height, body weight, BMI, waist circumference[d]				X			X		X		X		X		X
Complete physical examination[e]	X**														
Targeted physical examination[f]	X		X	X	X		X		X		X		X		X
Spontaneous AEs[g]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review of concomitant medications[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs: BP and HR[i]	X	X	X	X	X		X		X		X		X		X
Resting ECG (12-lead)[j]	X**			X							X				
Blood samples for clinical laboratory tests[k]	X**			X	X			X			X				
COVID-19 testing[l]	X			X							X				
Blood sample for prolactin[m]	X**			X							X				
Functional constipation inquiry[n]	X**	X	X	X	X				X		X			X	
Interim clinical observations[o]						X		X		X		X		X	
Determination of dose titration			X	X											
PK blood draw[p]			X	X					X						X
PANSS[q]	X			X	X		X		X		X		X		X
C-SSRS[r]	X**		X	X	X		X		X		X		X		X

DAY (± 3d, unless otherwise noted)	**1**	**3 (+1d)**	**8 (± 1d)**	**14 (± 2d)**	**28**	**42**	**56**	**70**	**84**	**98**	**102**	**116**	**130**	**154**	**168**
WEEK	**1**			**2**	**4[a]**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**
VISIT	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
TYPE OF VISIT	Clinic	Clinic	Clinic	Clinic	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic
PROCEDURE															
CGI-S scale	X			X	X		X		X		X		X		X
Cognition testing[s]	X[**]				X		X		X						X
SAS	X				X						X				
BARS	X				X						X				
AIMS	X				X						X				
AiCure registration and training	X														
KarXT dispensed and compliance evaluated[t]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EMA registration and training		X													
EMA[u]		X		X	X		X		X		X		X		X
Cognitive insight[v]					X		X		X		X		X		X
Digital biomarkers[w]		X	X	X	X		X		X		X		X		X

Table 2 Schedule of Assessments (Continued from Visits 16 to 30)

DAY (± 3d, unless otherwise noted)	182	196	210	224	238	252	266	280	294	308	322	336	350	364	371
WEEK	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52**	**53**
VISIT	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29 (EOT)**	**30 (EOS/ET/UNS[*])**
TYPE OF VISIT	Interim	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic	Clinic
PROCEDURE															
Urine pregnancy test (WOCBP only)[b]		X		X		X		X		X		X		X	X
Urine drugs of abuse and alcohol testing[c]		X		X		X		X		X		X		X	X
Height, body weight, BMI, waist circumference[d]		X		X		X		X		X		X		X	X
Complete physical examination[e]															X
Spontaneous AEs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review of concomitant medications[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs: BP and HR[i]		X		X		X		X		X		X		X	X
Resting ECG (12-lead)[j]		X						X						X	
Blood samples for clinical laboratory tests[k]		X						X						X	
COVID-19 testing[l]		X						X						X	
Blood sample for prolactin[m]		X						X						X	
Functional constipation inquiry[n]		X		X		X		X		X		X		X	X
Interim clinical observations[o]	X		X		X		X		X		X		X		
PK blood draw[p]														X	
PANSS[q]		X		X		X		X		X		X		X	X

DAY (± 3d, unless otherwise noted)	182	196	210	224	238	252	266	280	294	308	322	336	350	364	371
WEEK	26	28	30	32	34	36	38	40	42	44	46	48	50	52	53
VISIT	16	17	18	19	20	21	22	23	24	25	26	27	28	29 (EOT)	30 (EOS/ET/UNS*)
TYPE OF VISIT	Interim	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic	Clinic
PROCEDURE															
C-SSRS[r]		X		X		X		X		X		X		X	X
CGI-S scale		X		X		X		X		X		X		X	X
Cognition testing[s]						X						X			X
SAS		X						X						X	X
BARS		X						X						X	X
AIMS		X						X						X	X
KarXT dispensed and compliance evaluated[t]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
EMA[u]		X		X		X		X		X		X			
Cognitive insight[v]		X		X		X		X		X		X			
Digital biomarkers[w]		X		X		X		X		X		X			

Abbreviations: AE = adverse event; AIMS = Abnormal Involuntary Movement scale; BARS = Barnes Akathisia Rating Scale; BL = baseline; BMI = body mass index; BP = blood pressure; CGI-S = Clinical Global Impression–Severity scale; COVID-19 = coronavirus disease of 2019; C-SSRS = Columbia-Suicide Severity Rating Scale; d = day; ECG = electrocardiogram; EMAW = EMA Wellness; EOS = end of study; EOT = end of treatment; ET = early termination; HR = heart rate; PANSS = Positive and Negative Syndrome Scale; PK = pharmacokinetic; QTcF = QT interval corrected by Fridericia; SAS = Simpson-Angus Rating Scale; UNS = unscheduled visit.

Note: See APPENDIX 3 for optional modifications to the schedule of assessments during a pandemic period when local or governmental guidelines impose physical distancing restrictions.

* Other assessments as needed.

** Results are recorded from Day 35 visit of Study KAR-007/KAR-009 except for cognition testing for which the results are recorded from Day 32 visit of Study KAR-007/KAR-009.

a. Beginning after Visit 5/Day 28, interim visits will be completed every 2 weeks with flexibility between the in-clinic visits, which will occur every month. For interim visits, either a Home Health Care nurse or the study site staff will visit the subject to complete the scheduled visit, in addition to the telemedicine visit. Also when needed, the sites will have the option to schedule a subject for an in-clinic visit.

b. A urine pregnancy test for WOCBP should be performed at scheduled visits. In case of positive urine pregnancy test result, the sample should be sent to central laboratory for further investigation.

c. A National Institute on Drug Abuse-5 (NIDA-5) urine drug screen (cannabinoids or marijuana, phencyclidine, amphetamines, opiates, and cocaine) and test for alcohol (breathalyzer or blood alcohol level) will be performed at scheduled visits.

d. Height is recorded from Study KAR-007/KAR-009.

e. A complete physical examination includes body temperature (°C), general appearance, head/eyes/ears/nose/throat (HEENT), examination of thorax and,

assessment of cardiac, musculoskeletal, and circulatory systems, palpations for lymphadenopathy, and limited neurological examination.

f. A targeted physical examination includes at a minimum body temperature, a check of general appearance, as well as examination of organ systems that are relevant to the investigator based on review of the subject's reported AEs, review of systems, or concomitant medication use. These also include symptom-driven physical examinations which will be performed as clinically indicated at any study visit.

g. A part of interim clinical observations. For interim visits, spontaneous AEs will be reviewed by telemedicine over telephone or through video chat. Adverse events as reported by subjects or observed by clinical staff and occurs after dosing. One PK blood sample may be drawn if a relevant/significant AE (based on medical judgment) is reported during a scheduled visit or if there is a dose titration or a relevant/significant AE reported during an unscheduled visit (no multiple draws).

h. For interim visits, concomitant medications will be reviewed by telemedicine over telephone or through video chat if the Home Health Care nurse performs the visit.

i. Vital signs measurements should be taken at scheduled in-clinic visits, while the subject is supine and standing after 2 minutes. BP includes systolic and diastolic BP and is to be taken in the same arm for the duration of the study. During clinic visits, beginning with Day 1, orthostatic vital signs should occur 2 (±1) hours after morning dosing whenever possible.

j. ECG will be obtained within 1 to 2 hours post morning dose. ECG at all scheduled visits will be performed before blood withdrawal for any safety laboratory tests and/or PK analysis. ECGs will be transmitted electronically to a central reader for determination of ventricular rate (bpm), PR (msec), QRS (msec), QT (msec), QTcF (msec) measurements, and any other results.

k. Refer to Section 11.6 for individual laboratory tests.

l. Optional COVID-19 testing may be performed at an unscheduled visit based on the investigator's discretion. If a subject tests positive for COVID-19 during the study, he/she may be quarantined and any scheduled visits should be rescheduled at the discretion of the investigator. If the subject requires hospitalization, an SAE should be reported and the subject should be followed up as per Section 11.7.4.

m. Blood sample for prolactin should be collected in the morning predose at scheduled visits.

n. Functional constipation inquiry: At specified visit, subjects will be asked whether they have experienced constipation (per the ROME III criteria and Bristol Stool Form Scale; see APPENDIX 2) since the last visit and if yes, whether the constipation required intervention. If the subject answers yes, sites are instructed to ask subjects to provide event date and ensure the event is documented as an AE and treatment is documented as concomitant medication.

o. Interim clinical observations include: collection of vital signs, review of spontaneous AEs and concomitant medications. These assessments will be performed by a Home Health Care nurse and/or telemedicine over telephone or through video chat.

p. PK blood samples will be collected in the morning before dosing on Days 8, 14, 84, 168 and 364. On Days 8 and 14, three PK samples will be collected at pre-dose in the morning, 1 hour (±5 min), and 2 hours (±10 min) postdose. For Days 84, 168, and 364, a single sample before the morning dose will be collected. Note: In cases of dose reduction, re-escalation or re-titration, additional PK samples will be collected at 8 and 14 days post dose reduction, re-escalation, or re-titration in accordance with the Visits 3 and 4 schedules, respectively, and the original PK sampling schedule will be followed thereafter.

q. It is recommended, if at all possible, that the PANSS assessment should be performed before all the other scale assessments for all visits at which it is performed. The PANSS assessment includes the Marder Factor.

r. The "since last visit" version should be used for C-SSRS administration. At the Unscheduled visit, the C-SSRS should be performed to monitor subjects for suicidality.

s. Cognition testing is performed using CANTAB. Cognition testing should not be done within 8 hours of receiving a benzodiazepine or sleep medication. Cognition testing at Visit 30 will only be performed if the visit is a result of Early Termination of a subject.

t. See Pharmacy Manual for details on KarXT dispensing and compliance evaluation.

u. EMA will be completed by the subject at home on a cellular device 3 times per day for 7 days every 28 days, beginning on Day 29. An abbreviated

version of the assessment will be utilized on Days 4-6 and 15-17 to familiarize subjects with the process.

v. Cognitive insight will be completed by the subject at home on a cellular device 1 time per day for 3 days every 28 days beginning on Day 32. Refer to Study Operational Manual for details.

w. Digital biomarkers of schizophrenia will be calculated through completion of a smartphone-based assessment daily by the subject for 3 days collected initially on Days 4-6, 9-11, and 15-17. Subsequently subjects will complete assessments daily for 3 days every 28 days, beginning on Day 29.

10.1 Informed Consent

Informed consent forms must be approved for use by the reviewing Independent Ethics Committee (IEC)/Institutional Review Board (IRB). Before performing any study-related procedures, the investigator (or designee) will obtain written informed consent from the subject and/or caregiver.

10.2 Study Procedures

Assessments and their timing are to be performed as outlined in the Schedule of Assessments (Table 2). Section 11.6 specifies laboratory assessment samples to be obtained.

Assessments and procedures scheduled at a visit where KarXT is administered should be performed before administration of treatment unless otherwise indicated in the Schedule of Assessments (Table 2).

Safety assessments are described in Section 11 and include spontaneous AEs; SAEs and AEs leading to discontinuation of the KarXT; cholinergic symptoms; SAS; BARS; AIMS; body weight; BMI; waist circumference; orthostatic vital signs; ECG; clinical laboratory assessments (hematology, clinical chemistry, coagulation, urinalysis, and drug screen); physical examination; and C-SSRS.

Efficacy assessments are described in Section 12 and include PANSS and CGI-S scores.

PK assessments are described in Section 13 and include monitoring of trough concentrations of xanomeline and trospium.

Exploratory assessments are described in Section 14 and include cognition testing using CANTAB; prolactin levels; digital biomarkers of schizophrenia; EMA; and cognition insight.

The investigator may, at his/her discretion, arrange for a subject to have an unscheduled assessment, especially in the case of AEs that require follow-up or are considered by the investigator to be possibly related to the use of KarXT. The unscheduled visit page in the eCRF must be completed. The assessments and procedures that may be performed during an unscheduled visit are outlined in the Schedule of Assessments (Table 2). Additional assessments can be performed as needed, at the discretion of the investigator, and following discussion with the medical monitor.

Study discontinuation procedures are described in Section 8.4 and Section 8.6.

10.2.1 AiCure Adherence Technology

This study will employ a medication adherence monitoring platform (herein after referred to as Platform) for all subjects in the study. The Platform uses artificial intelligence on smartphones to confirm medication ingestion. In addition, built-in reminders and a communication system allow real-time intervention in case of drug interruptions.

Use of this Platform will in no way supersede or replace the physician and/or prescribed medication protocol of the subjects. Because the Platform does not change the medication protocol of the subjects, but rather encourages adherence to the predefined protocol, use of this Platform presents minimal risk to the subjects. Use of the Platform will be required for all subjects in the study.

The monitoring Platform requires that all subjects take each dose of the medication while using a smartphone. Participants will download the AiCure application on their personal smartphone device; for participants who do not have a smartphone or do not wish to use their personal smartphone, site personnel will provide the participant with one of the preloaded backup provisioned devices.

When at home, study subjects will receive a medication reminder at a time within a predefined window. This notification reminds subjects to take their medication dose while using the Platform. Subjects will follow a series of prescribed steps in front of the front-facing webcam to visually confirm their ingestion of the medication. The application on the smartphone will make an automated determination of whether the subject has properly taken their medication at the prescribed time. There is no need for a healthcare provider to review the administration, nor would a healthcare provider need to be available at the time the subject takes their medication. The amount of guidance that the device provides to the subject is automatically reduced as the subject becomes more proficient at using the application.

Digital Biomarker Assessment:

During the study, the AiCure Platform will also present additional material to subjects on their smartphone and record and analyze their responses. The material will be presented to subjects in one of two ways. In the first, material will be presented to subjects, and will include questionnaires provided at regular intervals during the study. Images may also be shown to subjects, and they will be asked to describe each image in a few sentences to the camera of the smartphone. This Digital Biomarker Assessment will only be conducted in some countries participating in the trial.

Data Collected on the AiCure Platform:

After the device confirms proper medication ingestion, video recordings will be encrypted and transmitted to a secure centralized location for further analysis, including testing for duplicate enrollment. Video and audio recordings from the Digital Biomarker assessments will be encrypted and transmitted in a similar manner. The captured data and video is reviewable through a roles and rules restricted system ensuring privacy of the information. The system is compliant with applicable US and European data privacy laws, including General Data Protection Regulation (GDPR) (EU) 2016/679 the Health Insurance Portability and Accountability Act (HIPAA), which protects the privacy and security of healthcare information.

Phone numbers of the patients may also be collected and stored in an encrypted manner. Storing the phone numbers will allow for direct communication with patients, including automated

messaging from the Platform device and contact by healthcare providers or other monitoring personnel. At no time is the phone number visible to healthcare providers or monitoring personnel. Individuals outside the clinical sites will not be provided with patient names, nor will they be given access to patient medical records.

The Platform may provide significant benefits to study subjects as well as to the other stakeholders in the trial. Subjects will benefit from rapid and tailored intervention in case of non-adherence (drug interruptions) without having to visit the clinic for unscheduled visits. Healthcare providers will have access to real-time and continuous adherence data without having to rely on self-reported data or frequent study visits by patients. Subjects who regularly fail to take their medication will be contacted by healthcare providers or other study monitoring personnel for retraining.

11 SAFETY ASSESSMENTS

Safety assessments (spontaneous AEs; SAEs and AEs leading to discontinuation of the KarXT; cholinergic symptoms; SAS; BARS; AIMS; body weight; BMI; waist circumference; orthostatic vital signs; ECG; clinical laboratory assessments [hematology, clinical chemistry, coagulation, urinalysis, and drug screen]; physical examination; and C-SSRS) will be performed at protocol-specified visits, as specified in the Schedule of Assessments (Table 2).

11.1 Demographics, Medical History, and Psychiatric History

Demographic data, and medical and psychiatric history will be recorded from the Phase 3, double-blind, acute study (KAR-007/KAR-009).

Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs on the eCRF in accordance with Section 11.7. All changes not present at baseline or described in the past medical history and identified as clinically noteworthy must be recorded as AEs.

11.2 Vital Signs

Orthostatic vital signs (systolic and diastolic BP and heart rate measurements) will be evaluated at the in-clinic visits indicated in the Schedule of Assessments (Table 2). All vital signs will be measured supine and standing after 2 minutes. Blood pressure measurements are to be taken in the same arm for the duration of the study. During treatment, beginning with Day 1, orthostatic vital signs should occur 2 (±1) hours after morning dosing, whenever possible.

Vital sign measurements will be repeated if clinically significant or machine/equipment errors occur. Out-of-range BP, or heart rate measurements will be repeated at the investigator's discretion. Any confirmed, clinically significant vital sign measurements must be recorded as AEs.

11.3 Complete/Targeted Physical Examination

A complete physical examination (body temperature, general appearance, head/eyes/ears/nose/throat [HEENT], examination of thorax and abdomen, assessment of cardiac, musculoskeletal, and circulatory systems, palpations for lymphadenopathy, and limited neurological examination) will be performed at visits as specified in Table 2. Physical examinations will be performed by a physician.

A targeted physical examination includes at a minimum body temperature, a check of general appearance, as well as examination of organ systems that are relevant to the investigator, based on review of the subject's reported AEs, review of systems, or concomitant medication use. These also include symptom-driven physical examinations which will be performed as clinically indicated at any study visit.

11.4 Weight, Height, Body Mass Index, and Waist Circumference

Height measurement will be recorded from the lead-in Study KAR-007 or KAR-009, weight, and waist circumference measurements will be obtained at visits as specified in Table 2. BMI should be calculated at these visits. All findings should be recorded in the eCRF.

11.5 Electrocardiograms

A 12-lead, resting ECG should be obtained within 1 to 2 hours post morning dose at the visits indicated in the Schedule of Assessments (Table 2). ECG at all scheduled visits will be performed before blood withdrawal for any safety laboratory tests and/or PK analysis.

ECGs will be transmitted electronically to a central reader for determination of ventricular rate (bpm), PR (msec), QRS (msec), QT (msec), QTcF (msec) measurements, and any other results. An assessment of normal or abnormal will be recorded; if the ECG is considered abnormal, the abnormality will be documented on the eCRF. ECGs will be repeated if clinically significant abnormalities are observed or artifacts are present.

11.6 Laboratory Assessments

Laboratory assessment samples (Table 3) are to be obtained at designated visits as detailed in the Schedule of Assessments (Table 2).

Table 3. Laboratory Assessments

Hematology	**Serum Chemistry**	**Urine Analysis (Dipstick)**
Full and differential blood count Hct Hb MCH MCHC MCV Platelet count RBC count WBC count with differential	Albumin ALT ALP AST Albumin Uric acid BUN or urea Carbon dioxide Creatinine Creatine kinase and subtypes Electrolytes (sodium, potassium, chloride, calcium, phosphorus) GGT Glucose LDH Total bilirubin Direct bilirubin Total cholesterol HDL LDL Triglycerides Total protein	Appearance pH Protein Glucose Ketone bodies Indicators of blood and WBCs Specific gravity Urobilinogen Occult blood WBCs
HbA1c	**Prolactin**	**COVID-19**
Coagulation		
PT Activated PTT Fibrinogen		
Pregnancy test: A urine pregnancy test for WOCBP should be performed at all scheduled visits. In case of positive urine pregnancy test result, a serum pregnancy test should be performed to confirm the result.		

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; COVID-19 = coronavirus disease of 2019; GGT = gamma-glutamyl transpeptidase; HCG = human chorionic gonadotropin; Hb = hemoglobin; Hct = hematocrit; HDL = high density lipoprotein; LDH = lactate dehydrogenase; LDL = low density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; WBC = white blood cell; WOCBP = women of childbearing potential.

Venous blood of approximately 12 to 20 mL will be withdrawn for the tests listed above at scheduled time points as per Table 2.

A minimum volume of 10 mL will be obtained to perform urinalysis and urine drug screen at scheduled time points as per Table 2.

Blood and urine samples will be analyzed at a central laboratory facility. Urine samples will be analyzed locally at investigator site by dipstick. If the dipstick indicates abnormality, the site will forward the sample to the central laboratory for further investigation. All laboratory reports must be reviewed, signed, and dated by the investigator. A legible copy of all reports must be filed with both the subject's eCRF and medical record (source document) for that visit. Any laboratory test result considered by the investigator to be clinically significant should be considered an AE (clinically significant AEs include those that require an intervention). Clinically significant abnormal values occurring during the study will be followed up until repeat test results return to normal, stabilize, or are no longer clinically significant.

All the study subjects will be closely monitored for the drug-induced liver toxicity (detailed in Section 11.7.5), during the study.

Other Laboratory Assessments:

- A National Institute on Drug Abuse-5 (NIDA-5) urine drug screen (cannabinoids or marijuana, phencyclidine, amphetamines, opiates, and cocaine) will be performed throughout the study.
- Alcohol testing will be performed using a breathalyzer or blood alcohol test.

11.7 Adverse Events

11.7.1 Adverse Events

An AE is any symptom, physical sign, syndrome, or disease that either emerges during the study or, if present at screening/baseline, worsens during the study, regardless of the suspected cause of the event. All medical and psychiatric conditions (except those related to the indication under study) present at screening/baseline will be documented in the medical history eCRF. Changes in these conditions and new symptoms, physical signs, syndromes, or diseases should be noted on the AE eCRF during the rest of the study. Clinically significant laboratory abnormalities should also be recorded as AEs. Surgical procedures that were planned before the subject enrolled in the study are not considered AEs if the conditions were known before study inclusion; the medical condition should be reported in the subject's medical history.

In accordance with the protocol, the investigator and/or study staff will elicit AEs and intercurrent illness during and at the end of the study period and these will be recorded on the appropriate page of the eCRF. Adverse events will be elicited by asking the subject a nonleading question, for example, "Have you experienced any new or changed symptoms since we last asked?" The eCRF will be completed at the end of the study as soon as the results of the final lab tests are available.

Each AE is to be documented on the eCRF with reference to date of onset, duration, frequency, severity, relationship to KarXT, action taken with KarXT, treatment of event, and outcome. Furthermore, each AE is to be classified as being serious or nonserious. Changes in AEs and resolution dates are to be documented on the eCRF.

For the purposes of this study, the period of observation for collection of AEs extends from the time immediately after the administration of KarXT on Day 1 until the EOS or ET. Follow-up of the AE, even after the date of therapy discontinuation, is required if the AE persists until the event resolves or stabilizes at a level acceptable to the investigator.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the event should be noted. If the intensity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

The severity of AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (Grades 1 through 5).

Specific guidelines for classifying AEs by intensity and relationship to KarXT are given in Table 4 and Table 5.

Table 4. Classification of Adverse Events by Intensity

MILD: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
MODERATE: An event that is sufficiently discomforting to interfere with normal everyday activities.
SEVERE: An event that prevents normal everyday activities.

Table 5. Classification of Adverse Events by Relationship to KarXT

UNRELATED: This category applies to those AEs that are clearly and incontrovertibly due to extraneous causes (disease, environment, etc).
UNLIKELY: This category applies to those AEs that are judged to be unrelated to the test drug but for which no extraneous cause may be found. An AE may be considered unlikely to be related to KarXT if or when it meets 2 of the following criteria: (1) it does not follow a reasonable temporal sequence from administration of the test drug; (2) it could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it does not follow a known pattern of response to the test drug; or (4) it does not reappear or worsen when the drug is readministered.
POSSIBLY: This category applies to those AEs for which a connection with the test drug administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related if or when it meets 2 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; or (3) it follows a known pattern of response to the test drug.
PROBABLY: This category applies to those AEs that the investigator feels with a high degree of certainty are related to the test drug. An AE may be considered probably related if or when it meets 3 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose (note that there are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists; for example, as in bone marrow depression, fixed drug eruptions, or tardive dyskinesia); or (4) it follows a known pattern of response to the test drug.
DEFINITELY: This category applies to those AEs that the investigator feels are incontrovertibly related to test drug. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic

factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose and recurs with re-exposure to drug (if rechallenge occurs); and (4) it follows a known pattern of response to the test drug.

Abbreviation: AE = adverse event.

11.7.2 Adverse Events of Special Interest

Adverse event of special interest is orthostasis and it will be monitored.

11.7.3 Serious Adverse Events

An SAE is any untoward medical occurrence, in the view of either the investigator or Sponsor, that:

- results in death,
- is life-threatening,
- results in inpatient hospitalization or prolongation of existing hospitalization (however, hospitalization for elective treatment of a pre-existing non-worsening condition is not considered an SAE; the details of such hospitalizations must be recorded on the medical history or physical examination page of the eCRF),
- results in persistent or significant disability/incapacity, and/or
- is a congenital anomaly/birth defect.

Other important medical events that may not be immediately life-threatening or result in death or hospitalization, based upon appropriate medical judgment, are considered SAEs if they are thought to jeopardize the subject and/or require medical or surgical intervention to prevent 1 of the outcomes defining an SAE. Serious AEs are critically important for the identification of significant safety problems; therefore, it is important to take into account both the investigator's and the Sponsor's assessment. If either the Sponsor or the investigator believes that an event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting.

11.7.4 Serious Adverse Event Reporting

An SAE occurring from the time the first dose of KarXT is administered, during the study, or within 1 week of stopping the treatment must be reported to the Catalyst Clinical Research Pharmacovigilance group and will be communicated to the Sponsor. Any such SAE due to any cause, whether or not related to the KarXT, must be reported within **24 hours of occurrence or when the investigator becomes aware of the event**. Notification can be made using email.

Catalyst Clinical Research Pharmacovigilance email address: [redacted]

The event must be recorded on the standard AE eCRF. Preliminary reports of SAEs must be followed up by detailed descriptions later on, including clear and anonymized photocopies of

hospital case reports, consultant reports, autopsy reports, and other documents when requested and applicable. SAE reports must be made whether or not the investigator considers the event to be related to the investigational drug.

Appropriate remedial measures should be taken to treat the SAE, and the response should be recorded. Clinical, laboratory, and diagnostic measures should be employed as needed in order to determine the etiology of the problem. The investigator must report all additional follow-up evaluations to the Catalyst Clinical Research Pharmacovigilance group within 24 hours of becoming aware of the additional information or as soon as is practicable. All SAEs will be followed up until the investigator and Sponsor agree the event is satisfactorily resolved.

Any SAE that is not resolved by the end of the study or upon discontinuation of the subject's participation in the study is to be followed up until it either resolves, stabilizes, returns to baseline values (if a baseline value is available), or is shown to not be attributable to the KarXT or procedures.

11.7.5 ***Drug-Induced Liver Injury***

The sponsor has incorporated the following for monitoring of drug-induced liver injuries:

- *An increase of serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) to >3 × ULN should be followed by repeat testing within 48 to 72 hours of all 4 of the usual serum measures (ALT, AST, ALP, and total bilirubin) to confirm the abnormalities and to determine if they are increasing or decreasing. An inquiry should be made about the symptoms (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, and rash).*
- *Close observation should be initiated with ALT or AST >3 × ULN:*
    - *Repeat liver enzyme and serum bilirubin tests 2 or 3 times weekly. The frequency of retesting can decrease to once per week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic.*
    - *Obtain a more detailed history of symptoms and prior or concurrent diseases.*
    - *Obtain a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.*
    - *Rule out acute viral hepatitis types A, B, C, D, and E, autoimmune or alcoholic hepatitis, non-alcoholic steatohepatitis, hypoxic/ischemic hepatopathy, and biliary tract disease.*
    - *Obtain a history of exposure to environmental chemical agents.*
    - *Obtain additional tests to evaluate liver function, as appropriate (eg, international normalized ratio, and/or direct bilirubin).*

- *Consider gastroenterology or hepatology consultations.*

- *Discontinuation of treatment should be considered if:*
  - *ALT or AST >8 × ULN*
  - *ALT or AST >5 × ULN for more than 2 weeks*
  - *ALT or AST >3 × ULN and (total bilirubin >2 × ULN or international normalized ratio >1.5)*
  - *ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (>5%)*

- *Hepatic adjudication of cases should include an evaluation for alternative causes such as viral, autoimmune, alcohol, hepatobiliary disorders, non-alcoholic steatohepatitis, concomitant medications, etc.*

- *Follow-up to resolution of elevated liver enzymes.*

- *Gamma-glutamyl transferase elevations alone should not prompt drug discontinuation.*

11.7.6 Suspected Unexpected Serious Adverse Reactions

Adverse events that meet all of the following criteria will be classified as suspected unexpected serious adverse reactions (SUSARs) and reported to the appropriate regulatory authorities in accordance with applicable regulatory requirements for expedited reporting:

- serious
- unexpected (ie, the event is not consistent with the safety information in the IB or package insert of generic trospium)
- there is at least a reasonable possibility that there is a causal relationship between the event and the study treatment

The investigator will assess whether an event is causally related to study treatment. The Sponsor (or Syneos Health) will consider the investigator's assessment and determine whether the event meets the criteria for being reportable as a 7-day or 15-day safety report. SUSARs that are fatal or life-threatening must be reported to the regulatory authorities and the IEC/IRBs (where required) within 7 days after the Sponsor (or Syneos Health) has first knowledge of them, with a follow-up report submitted within a further 8 calendar days. Other SUSARs must be reported to the relevant regulatory authorities and the IEC/IRBs within 15 calendar days after the Sponsor (or Syneos Health) first has knowledge of them.

The Sponsor (or Syneos Health) is responsible for reporting SUSARs and any other events required to be reported in an expedited manner to the regulatory authorities and for informing investigators of reportable events, in compliance with applicable regulatory requirements within specific timeframes. Investigators will notify the relevant IEC/IRBs of reportable events within the applicable timeframes.

Warnings and Precautions

Risk of Urinary Retention:

Trospium chloride tablets should be administered with caution to subjects with clinically significant bladder outflow obstruction because of the risk of urinary retention.

Angioedema:

Angioedema of the face, lips, tongue, and/or larynx has been reported with trospium chloride, the active ingredient in trospium chloride tablets. In one case, angioedema occurred after the first dose of trospium chloride. Angioedema associated with upper airway swelling may be life-threatening. If involvement of the tongue, hypopharynx, or larynx occurs, trospium chloride should be promptly discontinued and appropriate therapy and/or measures necessary to ensure a patent airway should be promptly provided.

Decreased Gastrointestinal Motility:

Trospium should be administered with caution to subjects with GI obstructive disorders because of the risk of gastric retention. Trospium chloride, like other antimuscarinic agents, may decrease GI motility and should be used with caution in subjects with conditions such as ulcerative colitis, intestinal atony, and myasthenia gravis.

Controlled Narrow-angle Glaucoma:

In subjects being treated for narrow-angle glaucoma, trospium chloride should only be used if the potential benefits outweigh the risks and in that circumstance only, with careful monitoring.

Central Nervous System Effects:

Trospium chloride is associated with anticholinergic CNS effects. A variety of CNS anticholinergic effects have been reported, including dizziness, confusion, hallucinations, and somnolence. Subjects should be monitored for signs of anticholinergic CNS effects, particularly after beginning treatment or increasing the dose. Advise subjects not to drive or operate heavy machinery until they know how trospium chloride affects them. If a subject experiences anticholinergic CNS effects, dose reduction or drug discontinuation should be considered.

Anticholinergic Adverse Reactions in Subjects with Moderate Renal Impairment:

Trospium is substantially excreted by the kidney. The effects of moderate renal impairment on systemic exposure are not known but systemic exposure is likely increased. Therefore, anticholinergic adverse reactions (including dry mouth, constipation, dyspepsia, urinary tract infection, and urinary retention) are expected to be greater in subjects with moderate renal impairment.

11.7.7 Pregnancy

WOCBP must have a negative pregnancy test at baseline (Day 1). Following administration of KarXT, any known cases of pregnancy in female subjects will be reported until the subject

completes or withdraws from the study. The pregnancy will be reported immediately by faxing/emailing a completed pregnancy report to the Sponsor (or designee) within 24 hours of knowledge of the event. The pregnancy will not be processed as an SAE; however, the investigator will follow-up with the subject until completion of the pregnancy and must assess the outcome in the shortest possible time, but not more than 30 days after completion of the pregnancy. The investigator should notify the Sponsor (or designee) of the pregnancy outcome by submitting a follow-up pregnancy report. If the outcome of the pregnancy involved spontaneous or therapeutic abortion (any congenital anomaly detected in an aborted fetus is to be documented), stillbirth, neonatal death, or congenital anomaly, the investigator will report the event by faxing/emailing a completed pregnancy report form to the Sponsor (or designee) within 24 hours of knowledge of the event. This event is considered as an SAE.

If the investigator becomes aware of a pregnancy occurring in the partner of a subject participating in the study, the pregnancy should be reported to the Sponsor (or designee) within 24 hours of knowledge of the event. Information regarding the pregnancy must only be submitted after obtaining written consent from the pregnant partner. The investigator will arrange counseling for the pregnant partner by a specialist to discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

Upon discontinuation from the study, only those procedures that would not expose the subject to undue risk will be performed. The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a subject is subsequently found to be pregnant after inclusion in the study, any pregnancy will be followed to term, and the status of mother and child will be reported to the Sponsor after delivery.

11.7.8 Overdose

The investigator must immediately notify the Sponsor of any occurrence of overdose with KarXT (total daily dose greater than 250/60 mg).

Signs and symptoms of overdose may vary considerably. They are usually manifested by increasing GI stimulation with epigastric distress, abdominal cramps, diarrhea and vomiting, excessive salivation, pallor, cold sweating, urinary urgency, blurring of vision, and eventually fasciculation and paralysis of voluntary muscles. Miosis, increases or decreases in blood pressure with or without bradycardia, and severe anxiety and panic may occur.

Supportive treatment should be used as indicated (artificial respiration, maintenance of airway, oxygen, etc). Atropine sulfate should be available for IV or intramuscular administration. Several doses ranging from 0.5 to 2.0 mg may be required. Epinephrine 0.1 to 1.0 mg subcutaneous may also be of value in overcoming severe cardiovascular or bronchoconstrictor responses.

Adverse events associated with overdoses should be reported on the eCRF.

11.8 Simpson-Angus Rating Scale

The SAS is an established instrument to measure drug-related extrapyramidal syndromes. It is a 10-item testing instrument used to assess gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, head dropping, glabella tap, tremor, and salivation. The range of scores is from 0 to 40 with increased scores indicating increased severity.

11.9 Barnes Rating Scale for Akathisia

The Barnes Rating Scale for akathisia is a rating scale used to assess the severity of drug-induced akathisia, or restlessness, involuntary movements and inability to sit still. The range of scores is 0 to 14, with higher scores indicating greater severity.[23]

11.10 Abnormal Involuntary Movement Scale

The AIMS is a rating scale that is used to measure involuntary movements know as tardive dyskinesia, which can sometimes develop as a side effect of long-term treatment with antipsychotic medications. It is a 12-item scale to assess orofacial, extremity, and truncal movements as well as the overall severity, incapacitation, and the subject's level of awareness of the movements. Items are scored from 0 (none) to 4 (severe). A higher score indicates more severe dyskinesia.

11.11 Columbia-Suicide Severity Rating Scale

The C-SSRS is a tool designed to systematically assess and track suicidal AEs (suicidal behavior and suicidal ideation) throughout the study.[24] The strength of this suicide classification system is in its ability to comprehensively identify suicidal events while limiting the over-identification of suicidal behavior. The scale takes approximately 5 minutes to administer. The C-SSRS will be administered by a trained rater at the site.

This study will utilize 2 versions of the C-SSRS. At the screening visit, the baseline/screening version will be completed; for all subsequent visits the "Since Last Visit" version of the C-SSRS will be administered.

11.12 Functional Constipation Inquiry

Constipation refers to bowel movements that are infrequent or hard to pass.[25] The stool is often hard and dry.[26] Other symptoms may include abdominal pain, bloating, and feeling as if one has not completely passed the bowel movement.[27] The normal frequency of bowel movements in adults is between 3 per day and 3 per week.[25] Constipation will be defined per the Rome III criteria, as less than 3 bowel movements per week, APPENDIX 2 (Longswreth,1486,C3).[28]

The Bristol Stool Form Scale has been correlated with a change in intestinal function, and has been shown to be a useful tool in clinical practice and research.[29] A sample Bristol Stool Form Scale is located in APPENDIX 2.

As a measure of anticholinergic effects, at each visit, subjects will be asked whether they have experienced constipation per the ROME III criteria since the last visit, and if yes, whether the constipation required intervention. If the subject answers yes, sites are instructed to ask subjects to provide event date and ensure event is documented as an AE and treatment is documented as concomitant medication. Subjects will not be required to collect and present their stool sample, nor will clinic staff be required to corroborate the subject assessment.

Additional attention can be given to other complaints as well including: straining with bowel movements, excessive time needed to pass a bowel movement, hard stools, pain with bowel movements secondary to straining, abdominal pain, abdominal bloating, and the sensation of incomplete bowel evacuation.[27, 30]

Treatment of constipation depends on the underlying cause and the duration that it has been present. For the purposes of constipation complaints during a clinical trial, the use of laxatives of a bulk forming agent, osmotic agent, stool softener, or lubricant type may be used.

As definitions of constipation are typically based on a history of at least a week, site physician discretion will be allowed for initiation of such treatments.

12 EFFICACY ASSESSMENTS

The Schedule of Assessments (Table 2) outlines the efficacy assessments to be performed throughout the study and their timing.

12.1 Positive and Negative Syndrome Scale

The PANSS is a clinician-administered scale used for measuring symptom severity of subjects with schizophrenia and is widely used in the study of antipsychotic therapy.[31] The PANSS rating form contains 7 positive symptom scales, 7 negative system scales, and 16 general psychopathology symptom scales. Subjects are rated from 1 to 7 on each symptom scale. The positive symptoms in schizophrenia are the excess or distortion of normal function such as hallucinations, delusions, grandiosity, and hostility, and the negative symptoms in schizophrenia are the diminution or loss of normal functions. It takes approximately 45 to 50 minutes to administer. PANSS total score is the sum of all scales with a minimum score of 30 and a maximum score of 210.

It is recommended, if at all possible, that the PANSS assessment should be performed before all the other scale assessments for all visits at which it is performed.

12.2 Clinical Global Impression-Severity

The CGI-S is a rating scale, completed independently by a clinician that is used to measure illness and symptom severity in subjects with mental disorders. It is used to rate the severity of a subject's illness at the time of assessment. The CGI-S modified asks the clinician 1 question: *"Considering your total clinical experience, how mentally ill is the subject at this time?"* The clinician's answer is rated on the following 7-point scale: 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill subjects.[32]

This rating is based upon observed and reported symptoms, behavior, and function in the past 7 days. As symptoms and behavior can fluctuate over a week, the score should reflect the average severity level across the 7 days.

13 PHARMACOKINETICS

13.1 Pharmacokinetic Sampling

13.1.1 Blood Samples

Blood samples for the analysis of xanomeline and trospium levels will be collected at the time points indicated in the Schedule of Assessments (Table 2). Approximately 4 ml of blood will be collected at each scheduled time point. The actual date and time of each blood sample collection will be recorded.

On Days 8 and 14, a total of 3 PK samples will be collected at pre-dose in the morning, 1 hour (±5 min), and 2 hours (±10 min) after the morning dose. For Days 84, 168, and 364, a single sample before the morning dose will be collected.

Note: In case of dose reduction, re-escalation, or re-titration, additional PK samples will be collected at 8 and 14 days post dose reduction, re-escalation, or re-titration in accordance with the Visits 3 and 4 schedules, respectively, and the original PK sampling schedule will be followed thereafter. Should the use of visit windows be necessary, PK sampling must accompany the actual day of potential up-titration for Visit 3/Day 8.

Note: A single PK sample may be drawn (preferably in the morning) if a relevant/significant AE is reported during a scheduled visit, or if there is a dose adjustment or relevant/significant AE reported during an unscheduled visit (no multiple draws). For ET that is related to an AE, the collection of a PK blood sample is not optional and should be drawn.

Details of PK blood sample collection, processing, storage, and shipping procedures will be provided in a separate laboratory manual.

13.2 Pharmacokinetic Analytical Methodology

The concentration of trospium and xanomeline will be determined from the plasma PK samples using a validated analytical method. Details of the method validation and sample analysis will be included with the final clinical study report.

14 EXPLORATORY ASSESSMENTS

The exploratory assessments cognition testing, prolactin levels, EMA, and cognition insight will be performed at scheduled visits, as per the Schedule of Assessments (Table 2).

14.1 Cognition Testing - Cambridge Neuropsychological Test Automated Battery

The computerized CANTAB provides an objective measure of cognitive function correlated to neural networks. A short cognitive battery measuring core cognitive domains of impairment in schizophrenia (ie, as per Brief Assessment of Cognition Schizophrenia key cognitive domains) will be employed for this study, and it will take approximately 30 minutes to complete. These CANTAB tests meet MATRICS workshop criteria.[33] Subjects will perform the test on a provisioned iPad with data immediately uploaded to the CANTAB Connect cloud-based platform (WiFi permitting).

Cognition testing should not be done within 8 hours of receiving benzodiazepine or sleep medications.

Table 6. Cognitive Tests and Cognitive Domains Assessed by the Cambridge Neuropsychological Test Automated Battery

CANTAB Tests	MATRICS Cognitive Domain	Outcome Measures
Rapid visual information processing	Sustained attention/vigilance	**A' Prime:** Signal detection measure of how good the subject is at detecting the target sequence (string of three numbers); regardless of response tendency
Verbal recognition memory	Verbal memory and new learning	**Free Recall:** The total number of words that are correctly recalled from the presentation phase by the subject during the immediate free recall stage
Spatial Span	Working memory	**Forward Span Length:** The longest sequence of boxes successfully recalled by the subject
One-touch stockings of Cambridge	Executive Function Planning/Problem Solving	**Problems Solved on First Choice:** The total number of assessed trials where the subject chose the correct answer on their first attempt

Abbreviation: CANTAB = Cambridge Neuropsychological Test Automated Battery

14.2 Change in Prolactin

Blood samples to assess the change in prolactin levels will be obtained on scheduled visits as specified in Table 2. At each of these visits, blood sample must be collected before the morning dose of the KarXT, whenever possible.

14.3 Digital Biomarkers of Schizophrenia

Study subjects will be performing brief smartphone-based assessments using the AiCure application mentioned in Section 10.2.1. Video and audio of participant behavior captured during these assessments will be used to calculate visual and auditory markers of schizophrenia symptomatology. These digital biomarkers will be used as exploratory efficacy endpoints to measure change from baseline in disease severity. The following exploratory endpoints will be collected:

- Overall emotional expressivity
- Positive emotional expressivity
- Negative emotional expressivity
- Audio intensity / speech volume Fundamental frequency of voice
- Formant frequencies of voice
- Vocal jitter
- Vocal shimmer
- Pause lengths during speech
- Lexical diversity
- Rate of speech
- Euclidean head movement
- Rotational head movement

14.4 EMA Wellness Assessments

14.4.1 Ecological Momentary Assessment

EMA is an ambulatory data collection technique that allows the real-time in vivo assessment of functioning behaviors. In the present study, EMA will be used to assess the subject's functioning associated to negative symptoms and psychotic symptoms in schizophrenia through the use of smartphones.

EMA surveys are multiple choice questions about the subject's current location, if they are alone or with others, and activities and moods in the last hour. A pop-up visualization will signal participants, 3 times per day for 7 days, to respond to very brief (e.g., 3 minutes) questionnaires about their activities, mood, and symptom experiences during the last hour, per the Schedule of Assessments (Table 2). An abbreviated EMA survey, collecting only information on the subject's location, alone or with others, and activities and moods will be given 3 times per day for 3 days starting on Day 4 and Day 15. Daily assessment times will be adjusted to accommodate each subject's typical sleep and wake schedules.

14.4.2 Insight into Cognitive Performance

Insight assessment will be conducted through testing on the Verbal Learning and Memory Test (VLMT). This assessment will be performed 3 times per EMA week beginning on the 4th day of

each EMA week. During each VLMT administration, subjects will be presented with a list of words over 3 trials, 30 seconds per trial. The list lengths vary between 6-, 12-, or 18-items with 1 length per day and 3 different lengths during each EMA week. Immediately following each exposure to the list, subjects will be shown target and recognition foil words one-by-one and asked to indicate whether or not the word appeared on the list.

In order to examine response bias and the ability to self-evaluate memory performance, immediately after each recognition trial, the subjects will be asked to indicate how many words they believe that they got correct, with the response options ranging from 0-36 words. They will also be asked how well they did compared to the previous trial and at the end of the 3 trials they will be asked if they improved over the 3 learning trials.

14.4.3 Data Collected on EMAW Platform

Data are encrypted and uploaded to secure servers whenever the phone is connected to Wi-Fi or if cellular data is available. If a Wi-Fi and cellular data are unavailable, EMA response data will be transferred during in-clinic visits.

EMA assessments collect information about the subject's current location. This is defined with EMA prompts (home vs away and where if away); they will also be asked if they are alone or with others, and as being queried as to activities, symptoms, and moods in the last hour. Symptom scores will be reported as the severity score for each survey. The functioning behaviors reported during each survey will be recorded, and the symptom scores were time-linked to activities and locations at the time of assessment.

Negative symptoms ratings have been shown to converge excellently with 'where and who' responses. Thus, the outcomes variables for location will be the number of surveys answered as home alone, home with someone, away alone, and away with someone. Individual activities will be quantified in terms of the total number of surveys where each activity was endorsed and the percentage of total number of activities per survey represented by each activity. Symptom severity will be sampled at each survey and will be examined in terms of the number of surveys where psychosis severity exceeded the PANSS-related threshold of definitely present (4 or more).

Dependent variables for the insight assessment, the VLMT, are the number of correct identifications of target words per trial and a total score of correct identifications of targets and correct rejections of foils. The participants will also provide an immediate estimate of their memory task performance as soon as each recognition trial is over. Insight will be measured by the difference between objective performance on the task and self-reported number of words correct. The self-reported global impression of improvement over time will be related to actual improvement over the 3 learning trials and as well as self-reported accuracy at each assessment.

Performance will be linked to the EMA data over the course of the protocol, with objective and subjective performance predicted by 'who x where' as well as the presence of other symptoms at

the time of the assessment. Changes in response bias will be defined as increasing congruence between objective and subjective memory performance over the course of the study.

In order to perform a sophisticated examination of all survey data, EMA wellness (EMAW) will use a mixed model repeated measures analysis of variance (MMRM). EMAW will predict the time course of 'who x where' by entering Month (1-12), day (1-7) and survey (1-3) as the repeated factors and 'who x where' as the 4-level outcomes variable. EMAW will also predict the course of the mood and symptom variables similarly. In order to examine the interaction between 'who x where' and the course of symptoms, 'who and where' variables will be entered as predictors of the course of the mood and psychosis symptoms. EMAW will also examine the frequency of activities over the course of the protocol with an identical analysis model, examining 'who x where' and concurrent symptoms' effects on activities. Using predetermined criteria, EMAW will characterize activities as 'active vs. inactive' as well as 'productive vs unproductive' for more molar analyses.

15 STATISTICAL ANALYSIS

A statistical analysis plan (SAP) will be prepared after the protocol is approved. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. The SAP will serve as a complement to the protocol and supersedes it in case of differences.

The statistical evaluation will be performed using SAS® software version 9.4 or higher (SAS Institute, Cary, NC). All data will be listed, and summary tables will be provided. Summary statistics will be presented by dose group. For continuous variables, data will be summarized with the number of subjects (N), mean, standard deviation, median, minimum, and maximum by treatment group. For categorical variables, data will be tabulated with the number and proportion of subjects for each category by treatment group. No statistical hypothesis testing will be performed.

15.1 Determination of Sample Size

As the primary objective of this study is to assess the long-term safety and tolerability of KarXT, the number of subjects anticipated is based on the number of subjects recruited into and completing the acute studies (KAR-007, KAR-009) and meeting the eligibility requirements for KAR-008.

15.2 Analysis Populations

Enrolled population: All subjects who have given informed consent for KAR-008.

Safety population: All subjects who receive at least 1 dose of KarXT during the current study will be included in the safety population and will be used in the safety analysis.

Modified ITT (mITT) population: All subjects who are enrolled, received at least 1 dose of KarXT, and have a valid PANSS assessment at baseline of the acute study and at baseline of KAR-008 will be included in the mITT population and will be used in the efficacy analysis.

PK population: All subjects who have received at least 1 dose of KarXT and have at least 1 measurable plasma concentration of KarXT will be included in the PK population.

15.3 Safety Analysis

Safety endpoints will be summarized for all subjects in the Safety population. The presentation of safety data will be based on the treatment received in KAR-008.

All reported AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.1 or higher. The incidence of TEAEs (defined as events with an onset date on or after the first dose of KarXT) will be summarized by System Organ Class and Preferred Term. All AEs will be listed by subject, along with information regarding onset, duration, relationship and severity to KarXT, action taken with KarXT, treatment of event, and outcome.

Orthostatic vital signs, clinical laboratory data, prolactin levels, ECG parameters, and physical examinations will be summarized using descriptive statistics, including observed and change from baseline values, as well as numbers of subjects with values outside limits of the normal range at each time point. Similar descriptive summaries will be provided for C-SSRS, SAS, BARS, AIMS, body weight, BMI, and waist circumference.

15.4 Efficacy Analysis

Efficacy analyses will be summarized based on the mITT population. The summaries described in this section will provide data on maintenance of effect of open-label KarXT over 52 weeks. As these variables are summarized over time and the initial values can be impacted by the treatment received in the acute study, the presentation will use a combination of acute/extension study treatment groups, which is intended to provide perspective on the change in these values from the acute study through the treatment period of KAR-008. Tabular presentations will display descriptive statistics for Baseline of the acute study and the observed and change from baseline study results by scheduled visit for KAR-008.

Responder efficacy variables (PANSS responders) will be summarized descriptively. Response will be derived relative to the acute study Baseline assessment.

Continuous efficacy variables based on the change from baseline (PANSS, CGI-S) will be summarized using descriptive statistics by scheduled visit. Tabular presentations will display descriptive statistics for the Baseline of the acute study and the observed and change from baseline results by scheduled visit for KAR-008. Figures for selected variables will also be generated in order to demonstrate the kinetics of response over time.

15.5 Pharmacokinetic Analysis

Plasma concentrations of xanomeline and trospium will be listed for all subjects. The profiles or time points obtained with protocol deviations affecting PK results will be flagged and may be excluded from summaries and analyses.

The data will be presented graphically via individual plots and mean plots summarized by visit, and time point.

15.6 Exploratory Analysis

Change in cognition using CANTAB, digital biomarkers of schizophrenia, EMA, and cognition insight will be summarized using descriptive statistics.

Further details will be provided in the SAP.

15.7 Interim Analysis

No interim analysis is planned for this study.

15.8 Handling of Missing Data

For responder efficacy variables (PANSS responders), missing data may be handled by non-responder imputation, meaning that subjects who discontinue early or who have missing data at a given time point are imputed as though they did not achieve the given response. Supportive summaries will be based on observed case data.

For continuous efficacy variables based on the change from baseline (PANSS, CGI-S), summaries will be based on observed case data.

Additional methods of missing data imputation may be explored, and will be outlined in the SAP.

16 STUDY MANAGEMENT

16.1 Approval and Consent

16.1.1 Regulatory Guidelines

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the US Code of Federal Regulations (CFR), in compliance with International Council for Harmonisation (ICH) and good clinical practice (GCP) guidelines, and all applicable local, state and federal government regulations and laws.

16.1.2 Institutional Review Board/Independent Ethics Committee

Conduct of the study must be approved by an appropriately constituted IEC/IRB. Approval is required for the study protocol, protocol amendments (if applicable), IB, ICFs, recruitment material and subject information sheets and other subject-facing material.

16.1.3 Informed Consent

For each study subject, written informed consent will be obtained before any protocol-related activities. As part of this procedure, the PI or designee must explain orally and in writing the nature of the study, its purpose, procedures, expected duration, alternative therapy available, and the benefits and risks involved in study participation. The subject should be informed that he/she may withdraw from the study at any time, and the subject will receive all information that is required by local regulations and guidelines for ICH. The PI will provide the Sponsor or its representative with a copy of the IEC-/IRB-approved ICF before the start of the study.

The ICF should be revised whenever there are substantial changes to procedures or when new information becomes available that may affect the willingness of the subject to participate. Revisions to the consent form required during the study must be approved by the Sponsor and IEC/IRB, and a copy of the revised consent form is provided to the Sponsor. For any updated or revised consent forms, the subjects must be re-consented for continued participation in the study.

A pregnant partner consent form should be obtained before collecting any data from a female pregnant partner of a male subject, if she becomes pregnant during the course of the study or within 1 week of the last dose of KarXT.

A caregiver consent must be obtained (Ukraine only) before collecting any data from a caregiver pertaining to him or her and the subject.

Subject Registry (for the US only):

Clinical trial registries, such as clinical trial subject database (CTSdatabase) and Verified Clinical Trials (VCT), seek to reduce duplicate enrollment by identifying potential protocol violations and duplicate subjects before randomization. At the time of providing the informed

consent for the study, the investigator or designee will explain the IRB-approved Subject Database Authorization to the subject and witness the signature.

On Day 1 before any other study procedures, site staff that have received training and login information access (www.ctsdatabase.com) to the database will enter the subject study ID number and authorized subject identifiers. Two reports, one from CTS and one from VCT, detailing any potential protocol violations or dual enrollment attempts will be generated and should be printed for source documentation. The report will detail each protocol violation detected and specific washout period dates where applicable. Participants who are identified as verification failures by CTS or VCT should not be enrolled without documented approval from Karuna or Syneos Health.

At the last subject contact, CTSdatabase and VCT staff will automatically close out the subject (safety follow-up, ET, or completer) based on interactive response system (IXRS).

Verified Clinical Trial Registry (for Ukraine only):

At participating sites in Ukraine, VCT will be used to verify participants' current and past research study status in order to mitigate safety concerns associated with duplicate enrollment and protocol deviations associated with multiple trial enrollment. Following proper regionally compliant informed consent and after obtaining a subject number from IXRS, each participant will be checked in the VCT database. Partial identifiers will be utilized. Participants who are identified as verification failures by VCT should not be enrolled without documented approval from Karuna or Syneos Health.

16.2 Data Handling

Any data to be recorded directly on the eCRFs (to be considered as source data) will be identified at the start of the study. Data reported on the eCRF that are derived from source documents should be consistent with the source documents, or the discrepancies must be explained. See also Section 16.3.

Clinical data will be entered by site personnel on eCRFs for transmission to the Sponsor. Data on eCRFs transmitted via the web-based data system must correspond to and be supported by source documentation maintained at the study site, unless the study site makes direct data entry to the databases for which no other original or source documentation is maintained. In such cases, the study site should document which eCRFs are subject to direct data entry and should have in place procedures to obtain and retain copies of the information submitted by direct data entry. All study forms and records transmitted to the Sponsor must only include coded identifiers such that directly identifying personal information is not transmitted. The primary method of data transmittal is via the secure, internet-based electronic data capture (EDC) system maintained by Syneos Health. Access to the EDC system is available to only authorized users via the study's secure internet web site, where a user unique assigned username and password are required for access.

Any changes made to data after collection will be made through the use of the EDC system. Electronic CRFs will be considered complete when all missing and/or incorrect data have been resolved.

16.3 Source Documents

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. The investigator will provide direct access to source documents and/or source data in the facilitation of trial-related monitoring, audits, review by IECs/IRBs, and regulatory inspections.

The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, not obscure the original entry, and be explained if necessary.

Data recorded on source documents will be transcribed onto eCRFs. Copies of completed eCRFs will be provided to the Sponsor and the sites at the end of the study. The completed eCRFs will be retained by the investigator.

16.4 Record Retention

Study records and source documents must be preserved for at least 15 years after the completion or discontinuation of/withdrawal from the study, at least 2 years after the drug being studied has received its last approval for sale, or at least 2 years after the drug development has stopped, and in accordance with the applicable local privacy laws, whichever is the longer time period.

The investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of subject health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR, Parts 160 and 164 (the HIPAA of 1996 Privacy Regulation). The investigator shall ensure that study subjects authorize

the use and disclosure of protected health information in accordance with HIPAA Privacy Regulation and in a form satisfactory to the Sponsor.

16.5 Monitoring

The study will be monitored according to the KAR-008 monitoring plan to ensure that it is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements.

Monitoring visits, on-site and remote (telephone) or a combination and contacts will be made at appropriate times during the study. The PI will assure him/her and adequate site personnel are available throughout the study to collaborate with clinical monitors. Clinical monitors must have direct access to source documentation in order to check the completeness, clarity, and consistency of the data recorded in the eCRFs for each subject.

The investigator will make available to the clinical monitor all source documents and medical records necessary to review protocol adherence and eCRFs. In addition, the investigator will work closely with the clinical monitor and, as needed, provide them appropriate evidence that the study is being conducted in accordance with the protocol, applicable regulations, and GCP guidelines.

16.6 Quality Control and Quality Assurance

The Sponsor or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, security, and reliability of the study data presented to the Sponsor lies with the investigator generating the data.

The Sponsor will arrange audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the protocol, standard operating procedures, GCP, and all applicable regulatory requirements. Audits will be independent of and separate from the routine monitoring and quality control functions. Quality assurance procedures will be performed at study sites and during data management to assure that safety and efficacy data are adequate and well documented.

16.7 Protocol Amendment and Protocol Deviation

16.7.1 Protocol Amendment

Amendments to the protocol that entail corrections of typographical errors, clarifications of confusing wording, changes in study personnel, and minor modifications that have no effect on the safety of subjects or the conduct of the study will be classed as administrative amendments and will be submitted to the IEC/IRB for information only. Syneos Health will ensure that acknowledgement is received and filed. Amendments that are classed as substantial amendments must be submitted to the appropriate regulatory authorities and the IECs/IRBs for approval and will not be implemented at sites until such approvals are received, other than in the case of an urgent safety measure.

16.7.2 Protocol Deviations

Should a protocol deviation occur, the Sponsor must be informed as soon as possible. Protocol deviations and/or violations and the reasons they occurred will be included in the clinical study report. Reporting of protocol deviations to the IEC/IRB and in accordance with applicable regulatory authority mandates is an investigator's responsibility.

- All protocol deviations will be tracked in the eCRF/EDC system. Deviations considered major will be identified as such before study unblinding during medical monitor periodic review.

Major protocol deviations will be tabulated including the frequency and percentage of subjects with each type of deviation by treatment group.

16.8 Ethical Considerations

This study will be conducted in accordance with this protocol, the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the CFR; and in compliance with GCP guidelines.

IECs/IRBs will review and approve this protocol and the ICF. All subjects and/or caregivers are required to give written informed consent before participation in the study.

16.9 Financing and Insurance

Before the study commences, the Sponsor (or its designee) and the investigator (or the institution, as applicable) will agree on costs necessary to perform the study. This agreement will be documented in a financial agreement that will be signed by the investigator (or the institution signatory) and the Sponsor (or its designee).

The investigator is required to have adequate current insurance to cover claims for negligence and/or malpractice (US only). The Sponsor will provide no-exclusion insurance coverage for the clinical study as required by national regulations.

16.10 Publication Policy/Disclosure of Data

Both the use of data and the publication policy are detailed within the clinical study agreement. Intellectual property rights (and related matters) generated by the investigator and others performing the clinical study will be subject to the terms of a clinical study agreement that will be agreed between the institution and the Sponsor or their designee. With respect to such rights, the Sponsor or its designee will solely own all rights and interests in any materials, data, and intellectual property rights developed by investigators and others performing the clinical study described in this protocol, subject to the terms of any such agreement. In order to facilitate such ownership, investigators will be required to assign all such inventions either to their institution or directly to the Sponsor or its designee, as will be set forth in the clinical study agreement.

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18 APPENDICES

APPENDIX 1 CONTRACEPTION GUIDELINES

Women of childbearing potential (WOCBP) and men whose sexual partners are WOCBP must use at least 1 highly effective method of contraception during the study and for 7 days after the last dose of study treatment.

A woman is considered to be a WOCBP (fertile) following menarche and until becoming postmenopausal, unless she is permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

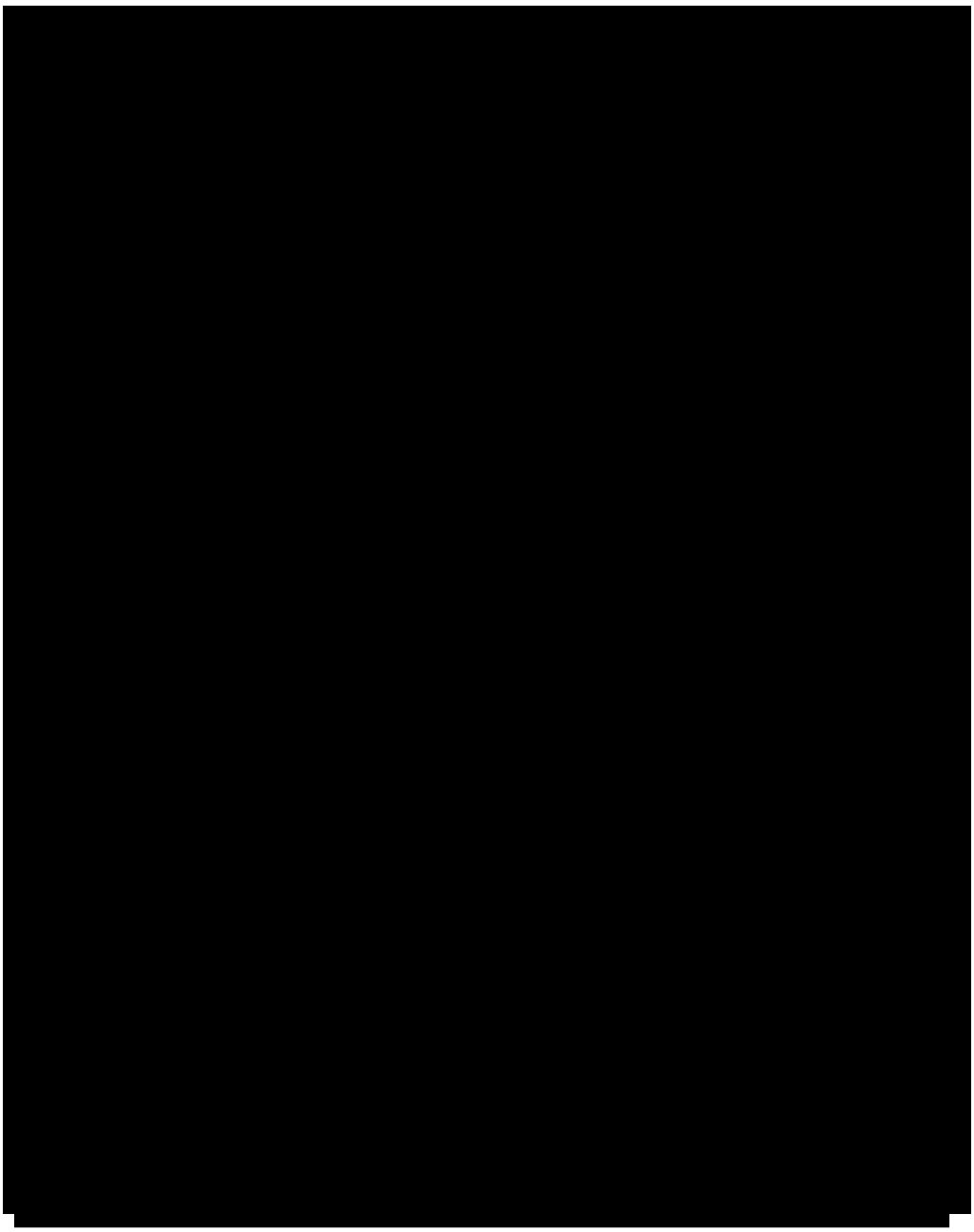
Highly effective methods of contraception are those which have a failure rate of <1% (when implemented consistently and correctly) and include:

- combined (containing estrogen and progestogen) hormonal contraception associated with inhibition of ovulation (administration may be oral, intravaginal, or transdermal)
- progestogen-only hormonal contraception associated with inhibition of ovulation (administration may be oral, injectable, or implantable)
- intrauterine device
- intrauterine hormone-releasing system
- bilateral tubal ligation or occlusion
- vasectomy (provided that the male has a medical assessment of surgical success)
- sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk in relation to the duration of the clinical trial, in line with the preferred and usual lifestyle of the subject)

All subjects will be strongly advised that they (or the female partners of male subjects should not become pregnant while on study treatment or for 7 days after the last dose). A female subject will be advised that she must report immediately to the study site for pregnancy testing and appropriate management in the event that she may be pregnant.

Reference: [HMA] Heads of Medicines Agencies. Clinical Trial Facilitation Group page. Recommendations related to contraception and pregnancy testing in clinical trials. http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf. September 15, 2014. Accessed April 8, 2020.

APPENDIX 2 FUNCTIONAL CONSTIPATION INQUIRY



APPENDIX 3. ALTERNATIVE PROCEDURES DURING COVID-19 PANDEMIC-RELATED PHYSICAL DISTANCING

The table below (Alternative Schedule of Assessments) outlines the timing of procedures and assessments to be performed remotely at scheduled visits during COVID-19 pandemic-related physical distancing. During this situation, all the in-clinic visits will be performed remotely, either a Home Health Care nurse or the study site staff will visit the subject to complete the scheduled visit. In addition to augment the remote visit, the telemedicine can be used.

Alternative Schedule of Assessments

DAY (± 3d, unless otherwise noted)	56	84	102	130	168	196	224	252	280	308	336	
WEEK	8	12	16	20	24	28	32	36	40	44	48	
VISIT	7R	9R	11R	13R	15R	17R	19R	21R	23R	25R	27R	UNS-R[a]
TYPE OF VISIT	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote
PROCEDURE												
Urine pregnancy test (WOCBP only)[b, #]	X	X	X	X	X	X	X	X	X	X	X	X
Urine drugs of abuse and alcohol testing[c, #]	X	X	X	X	X	X	X	X	X	X	X	X
Height, body weight, BMI, waist circumference[d, #]	X	X	X	X	X	X	X	X	X	X	X	X
Spontaneous AEs[e, ##]	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*
Review of concomitant medications[f, ##]	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*
Blood samples for clinical laboratory tests[g, #]			X			X			X			
COVID-19 testing[h, #]			X			X			X			
Blood sample for prolactin[i, #]			X			X			X			
Functional constipation inquiry[j, ##]	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*
Clinical observations[k, #]	X	X	X	X	X	X	X	X	X	X	X	X
KarXT dispensed and compliance evaluated[l, #]	X	X	X	X	X	X	X	X	X	X	X	
PK blood draw[m, #]		X			X							
PANSS[n,##]	X**	X**	X**	X**	X**	X**	X**	X**	X**	X**	X**	X**
C-SSRS[o, ##]	X**	X**	X**	X**	X**	X**	X**	X**	X**	X**	X**	X**
CGI-S[##]	X**	X**	X**	X**	X**	X**	X**	X**	X**	X**	X**	X**
BARS[##]			X**			X**			X**			X**
AIMS[##]			X**			X**			X**			X**
EMA[p]	X	X	X	X	X	X	X	X	X	X	X	
Cognitive insight[q]	X	X	X	X	X	X	X	X	X	X	X	
Digital biomarkers of schizophrenia[r]	X	X	X	X	X	X	X	X	X	X	X	

Abbreviations: AE = adverse event; AIMS = Abnormal Involuntary Movement scale; BARS = Barnes Akathisia Rating Scale; BMI = body mass index; BP = blood pressure; CGI-S = Clinical Global Impression–Severity scale; COVID-19 = Coronavirus Disease of 2019; C-SSRS = Columbia-Suicide Severity Rating Scale; d = day; EMA = ecological momentary assessment; HR = heart rate; PANSS = Positive and Negative Syndrome Scale; PK = pharmacokinetic; R = remote; UNS = unscheduled visit.

[#] This procedure will be performed either by a Home Health Care nurse or the study site staff.

[##] This procedure will be performed by telemedicine over a telephone or through video chat

[*] Procedure conducted by telemedicine over telephone or through video chat.
[**] Procedure conducted by telemedicine through video chat only (telephone assessment will not be permitted).

a. Other assessments as needed.
b. A urine pregnancy test for WOCBP should be performed at scheduled visits. In case of positive urine pregnancy test result, the sample should be sent to central laboratory for further investigation.
c. A National Institute on Drug Abuse-5 (NIDA-5) urine drug screen (cannabinoids or marijuana, phencyclidine, amphetamines, opiates, and cocaine) and test for alcohol (breathalyzer or blood alcohol level) will be performed at scheduled visits.
d. Height is recorded from Study KAR-007/KAR-009.
e. A part of interim clinical observations. AEs as reported by subjects or observed by clinical staff and occurs after dosing. Spontaneous AEs will be reviewed by telemedicine over telephone or through video chat. One PK blood sample may be drawn if a relevant/significant AE (based on medical judgment) is reported during a scheduled visit or if there is a dose titration or a relevant/significant AE reported during an unscheduled visit (no multiple draws).
f. Concomitant medications will be reviewed by telemedicine over telephone or through video chat if the Home Health Care nurse performs the visit.
g. Refer to Section 11.6 for individual laboratory tests.
h. Optional COVID-19 testing may be performed at an unscheduled visit based on the investigator's discretion.
i. Blood sample for prolactin should be collected in the morning predose at scheduled visits.
j. Functional constipation inquiry: At specified visits, subjects will be asked whether they have experienced constipation (per the ROME III criteria and Bristol Stool Form Scale; see APPENDIX 2) since the last visit and if yes, whether the constipation required intervention. If the subject answers yes, sites are instructed to ask subjects to provide event date and ensure the event is documented as an AE and treatment is documented as concomitant medication.
k. Clinical observations include: collection of vital signs, review of spontaneous AEs, and concomitant medications. These assessments will be performed by a Home Health Care nurse and/or telemedicine over telephone or through video chat. Vital signs measurements should be measured at scheduled visits, while the subject is supine and standing after 2 minutes. BP includes systolic and diastolic BP and is to be taken in the same arm for the duration of the study. Beginning with Day 1, orthostatic vital signs should occur 2 (±1) hours after morning dosing whenever possible.
l. See Pharmacy Manual for details on KarXT dispensing and compliance evaluation.
m. A single PK blood sample will be collected in the morning before dosing on Days 84, 168.
n. It is recommended, if at all possible, that the PANSS assessment should be performed before all the other scale assessments for all visits at which it is performed. The PANSS assessment includes the Marder Factor.
o. The "since last visit" version should be used for C-SSRS administration. At the Unscheduled visit, the C-SSRS should be performed to monitor subjects for suicidality.
p. EMA will be completed by the subject at home on a cellular device 3 times per day for 7 days starting the day after the study visit.
q. Cognitive insight will be completed by the subject at home on a cellular device 1 time per day for 7 days starting the day after the study visit. Refer to study Operational Manual for details.
r. Digital biomarkers of schizophrenia will be calculated through completion of a smartphone-based assessment daily by the subject for 3 days after each remote study visit beginning the day after Visit 2.

1 FINAL CLINICAL STUDY PROTOCOL

Karuna Therapeutics

Protocol Title: An Open-label Extension Study to Assess the Long-term Safety, Tolerability, and Efficacy of KarXT in Subjects with DSM-5 Schizophrenia

Protocol Number: KAR-008

IND Number:	127471
EudraCT Number:	Not applicable
Name of Investigational Product:	KarXT
Phase of Development:	Phase 3
Indication:	Schizophrenia
Sponsor:	Karuna Therapeutics 33 Arch Street Suite 3110 Boston, MA 02110 Tel: [redacted] Email: [redacted]
Protocol Version:	2.0
Protocol Date:	23 Oct 2020

PROTOCOL APPROVAL SIGNATURES

Protocol Title: An Open-label Extension Study to Assess the Long-term Safety, Tolerability, and Efficacy of KarXT in Subjects with DSM-5 Schizophrenia

Protocol Number: KAR-008

This study will be conducted in compliance with the clinical study protocol (and amendments), International Council for Harmonisation (ICH) guidelines for current Good Clinical Practice (GCP), and applicable regulatory requirements.

Sponsor Signatory

[redacted]
Karuna Therapeutics

DocuSigned by:
[redacted]
Signature
10/26/2020
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 10/26/2020 | 9:05:16 PM PDT
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Karuna Therapeutics

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Date (DD-Mmm-YYYY)

Contract Research Organization Signatory

[redacted]
Syneos Health

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Signer Name: [redacted]
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INVESTIGATOR SIGNATURE PAGE

Protocol Title: An Open-label Extension Study to Assess the Long-term Safety, Tolerability, and Efficacy of KarXT in Subjects with DSM-5 Schizophrenia

Protocol Number: KAR-008

Confidentiality and Current Good Clinical Practice (GCP)/E6(R2) Compliance Statement

- I, the undersigned, have reviewed this protocol (and amendments), including appendices, and I will conduct the study as described in compliance with this protocol (and amendments), and relevant International Council for Harmonisation (ICH) guidelines including GCP and applicable regulatory requirements.
- I am thoroughly familiar with the appropriate use of the KarXT, as described in this protocol and any other information provided by Karuna Therapeutics including, but not limited to, the current investigator's brochure.
- Prior to initiating the trial, I will provide the independent ethics committee (IEC)/institutional review board (IRB) all items subject to review and will obtain a written and dated approval/favorable opinion. Once the protocol has been approved by the IEC/IRB, I will not modify this protocol without obtaining prior approval of Karuna Therapeutics and of the IEC/IRB. I will submit the protocol amendments and/or any informed consent form modifications to Karuna Therapeutics and the IEC/IRB, and approval will be obtained before any amendments are implemented.
- I ensure that all persons or party assisting me with the study are adequately qualified and informed about the Karuna Therapeutics KarXT and of their delegated study-related duties and functions as described in the protocol. I will supervise these delegated persons or parties in the conduct of this trial.
- I ensure that source documents and trial records that include all pertinent observations on each of the site's trial subjects will be attributable, legible, contemporaneous, original, accurate, and complete.
- I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all case report forms, laboratory samples, or source documents forwarded to the Sponsor. Clinical information may be reviewed by the Sponsor or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.
- Information developed in this clinical study may be disclosed by Karuna Therapeutics to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

<Name>

<Title>

Investigator Signature

Date (DD-Mmm-YYYY)

Institution

2 SYNOPSIS

Title of Study:	An Open-label Extension Study to Assess the Long-term Safety, Tolerability, and Efficacy of KarXT in Subjects with DSM-5 Schizophrenia
Protocol Number:	KAR-008
Investigators/Study Sites:	Approximately 30 study sites in the United States and 10 study sites in Ukraine
Phase of Development:	Phase 3
Objective(s):	**Primary Objective:** The primary objective of the study is to assess the long-term safety and tolerability of KarXT in subjects with a Diagnostic and Statistical Manual-Fifth Edition (DSM-5) diagnosis of schizophrenia. **Secondary Objective:** The secondary objective of this study is to assess the long-term efficacy and monitor trough concentrations of xanomeline and trospium after administration of KarXT in adults with a DSM-5 diagnosis of schizophrenia: • To evaluate the reduction in Positive and Negative Syndrome Scale (PANSS) total score • To evaluate the reduction in PANSS positive score • To evaluate the improvement in Clinical Global Impression-Severity (CGI-S) results • To evaluate the reduction in PANSS negative score • To evaluate the reduction in PANSS Marder Factor negative symptoms score • To measure trough concentrations of xanomeline and trospium after administration of KarXT in adults who are acutely psychotic with a DSM-5 diagnosis of schizophrenia **Exploratory Objective:** The exploratory objectives of this study are • To evaluate cognition with the Cambridge Neuropsychological Test Automated Battery (CANTAB) • To evaluate prolactin levels after administration of KarXT • To evaluate digital biomarkers of schizophrenia • To evaluate ecological momentary assessment administered patient reported outcomes (EMA PRO) in schizophrenia • To evaluate cognitive insight using an EMA administered verbal learning and memory test (EMA VLMT) in schizophrenia
Study Endpoints:	**Primary safety endpoint:** The primary safety endpoint is the incidence of treatment-emergent adverse events (TEAEs) **Secondary safety endpoints:** The secondary safety endpoints of the study are: • Incidence of serious TEAEs • Incidence of TEAEs leading to withdrawal

	• Secondary efficacy endpoints: • The secondary efficacy endpoints of the study are: • Change from baseline in PANSS total score at Week 52 • Change from baseline in PANSS positive score at Week 52 • Change from baseline in PANSS negative score at Week 52 • Change from baseline in PANSS Negative Marder Factor score at Week 52 • Change from baseline in CGI-S score at Week 52 • Percentage of PANSS responders (a 30% change in PANSS total score) at Week 52 **Other Endpoints:** Safety endpoints: The other safety endpoints of the study are: • Spontaneously reported adverse events of special interest (AESIs) • Spontaneously reported procholinergic and anticholinergic symptoms • Change from baseline in Simpson-Angus Rating Scale (SAS) • Change from baseline in Barnes Rating Scale for Akathisia (BARS) • Change from baseline in Abnormal Involuntary Movement Scale (AIMS) • Change from baseline in body weight, body mass index (BMI), waist circumference • Change from baseline in orthostatic vital signs (supine and standing after 2 minutes): blood pressure (systolic and diastolic) and heart rate • Change from baseline in clinical laboratory assessments (hematology, clinical chemistry, coagulation, urinalysis, and drug screen) • Change from baseline in 12-lead electrocardiogram (ECG) • Change from baseline in physical examination • Suicidal ideation scale with the use of Columbia-Suicide Severity Rating Scale (C-SSRS) Pharmacokinetic Endpoint: The pharmacokinetic endpoint of the study is measurement of trough plasma concentrations of xanomeline and trospium. Exploratory Endpoints: The exploratory endpoints of the study are: • Change from baseline in cognition measuring core domains of impairment in schizophrenia using CANTAB • Change from baseline in prolactin levels • Observed digital biomarkers of schizophrenia (US only) • Observed EMA PRO in schizophrenia (US only) • Observed cognitive insight using EMA VLMT in schizophrenia (US only)
Study Design:	This is a Phase 3 multicenter, 53-week, outpatient, open-label extension (OLE) study to evaluate the long-term safety, tolerability, and efficacy of KarXT in subjects with DSM-5 schizophrenia who previously completed the treatment period of one of the two Phase 3 double-blind studies,

	KAR-007 or KAR-009. The study consists of a 52-week OLE treatment phase and a 7-day (±3 days) safety follow-up/end-of-study visit after the last KarXT dose for subjects who complete the treatment phase and those who prematurely discontinue from the study. After written informed consent, subjects who have completed the KAR-007 or KAR-009 Phase 3 acute study and received the last dose of the study drug in that trial will be rolled over into the current OLE study. The assessments performed on Visit 10 (Day 35) of Studies KAR-007 or KAR-009 will be considered as baseline assessments along with any additional procedures that will be performed on Day 0 of the current study. Any scheduled Day 0 assessments that were not completed on Day 35 of the acute study (KAR-007 or KAR-009) must be completed on Day 0 of the current study. Day 0 of the current study should be completed on the same day as Day 35 of the acute study after all Visit 10 (Day 35) procedures of the prior study KAR-007 or KAR-009 have been completed. Twice daily dosing with KarXT will commence in the morning of Day 1. Subjects who did not complete the full treatment period, or who early terminated Study KAR-007 or KAR-009, will not be eligible to enroll in this long-term extension study. A total of up to 350 subjects are planned to be enrolled in this study (aged 18 to 65 years) across approximately 30 study sites in the United States and 10 study sites in Ukraine. In this OLE study, all subjects will receive KarXT for up to 52 weeks. Regardless of treatment assignment in the preceding Phase 3 acute study (KAR-007 or KAR-009), all subjects will start on a lead-in dose of KarXT 50/20 (50 mg xanomeline/20 mg trospium) 2 times per day (BID) for the first 2 days (Days 1 and 2), followed by KarXT 100/20 BID for the remainder of Week 1 (Days 3 to 7). At Visit 3 (Day 8), dosing will be titrated upwards to KarXT 125/30 BID unless the subject is continuing to experience adverse events (AEs) from the previous dose of KarXT 100/20 BID. All subjects who are increased to KarXT 125/30 BID, depending on tolerability, will have the option to return to KarXT 100/20 BID. Re-escalation to 125/30 BID or re-titration in cases in which the subject has been off KarXT for a longer period of time (at least a week) is allowed and will require a discussion between the principal investigator and the medical monitor. Additional changes to KarXT dosing (e.g., temporary dose reductions) may be permitted as clinically indicated upon approval by the medical monitor. Beginning after Visit 5/Day 28, remote interim visits will be completed with flexibility between in-clinic visits, approximately once every 4 weeks. For interim visits, either a Home Health Care nurse or the study site staff will visit the subject to complete the scheduled visit. To augment at-home visits, telemedicine should be used at the investigator's discretion to review any information collected during the in-home interim visit. Also, when needed the sites will have the option to schedule a subject for an in-clinic visit in lieu of a remote interim visit. A safety follow-up/end-of-study/early termination visit (Visit 30/Day 371 ±3 days) will be performed for all subjects after the last dose of KarXT.

	An Independent Safety Monitoring Committee will be responsible for periodically reviewing the safety data from this study and confirming that the study may continue.
Study Population:	**Inclusion Criteria:** Individuals must meet all of the following criteria to be included in the study: 1. Subject is aged 18 to 65 years, at time of enrollment into the preceding acute study (KAR-007/009). 2. Subject is capable of providing informed consent. a. A signed informed consent form must be provided before any study assessments are performed. b. Subject must be fluent in (oral and written) English (United States only) or local language (Ukraine only) to consent. 3. Subject has completed the treatment period on study drug (through Day 35 -2 days) of Studies KAR-007 or KAR-009. 4. Subject resides in a stable living situation, in the opinion of the investigator. 5. Subject has an identified, reliable informant/caregiver willing to be able to address some questions related to certain study visits, if needed. An informant/caregiver may not be necessary if the subject has been the patient of the investigator for ≥1 year. 6. Women of childbearing potential (WOCBP) or men whose sexual partners are WOCBP must be sexually abstinent (in line with their preferred and usual lifestyle) or willing and able to use at least 1 highly effective method of contraception during the study and for at least 7 days after the last dose of KarXT. Sperm donation is not allowed for 7 days after the final dose of KarXT. A female subject is considered to be a WOCBP after menarche and until she is in a postmenopausal state for 12 consecutive months or is otherwise permanently sterile (for which acceptable methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy). For the definition and list of highly effective methods of contraception, see Appendix 1. **Exclusion Criteria:** Subjects will be excluded from the study if 1 or more of the following criteria is/are applicable: 1. Risk for suicidal behavior during the study as determined by the investigator's clinical assessment and C-SSRS as confirmed by the following: a. Subject answers "Yes" to "suicidal ideation" Item 4 (active suicidal ideation with some intent to act, without specific plan) or Item 5 (active suicidal ideation with specific plan and intent) on the C-SSRS. b. Nonsuicidal self-injurious behavior is not exclusionary. 2. Any clinically significant abnormality, including any finding(s) from the physical examination, vital signs, ECG, or laboratory test at the end-of-treatment visit of Studies KAR-007 or KAR-009 that the investigator, in consultation with the medical monitor, would consider to jeopardize the safety of the subject. 3. Female subject is pregnant.

	4. If, in the opinion of the investigator (and/or Sponsor), subject is unsuitable for enrollment in the study or subject has any finding that, in the view of the investigator (and/or Sponsor), may compromise the safety of the subject or affect his/her ability to adhere to the protocol visit schedule or fulfill visit requirements. 5. Subjects with extreme concerns relating to global pandemics such as coronavirus disease 2019 (COVID-19) that preclude study participation. 6. Risk of violent or destructive behavior. 7. Subjects participating in another investigational drug or device trial or planning on participating in another clinical trial during the course of the study.
Planned Sample Size:	A total of approximately 350 subjects are planned to be enrolled in this study.
Investigational Therapy:	1. Fixed dose KarXT 50/20 BID (50 mg xanomeline/20 mg trospium) oral (Days 1 to 2) 2. Fixed dose KarXT 100/20 BID (100 mg xanomeline/20 mg trospium) oral (Days 3 to 7) 3. Fixed dose KarXT 125/30 BID (125 mg xanomeline/30 mg trospium) oral (Days 8 to 364, if tolerated)
Reference Therapy:	Not applicable.
Treatment Duration:	Total study duration is up to 53 weeks, including a 52-week treatment phase and a 7-day follow-up/end-of-study phase.
Safety assessments:	Spontaneous AEs including AESIs; procholinergic and anticholinergic symptoms, serious AEs (SAEs) and AEs leading to discontinuation of KarXT; SAS; BARS; AIMS; body weight; BMI; waist circumference; orthostatic vital signs; clinical laboratory assessments (hematology, clinical chemistry, coagulation, urinalysis, and drug screen); 12-lead ECG; physical examination; and C-SSRS will be evaluated throughout the study as scheduled.
Efficacy assessments:	PANSS total score, PANSS positive score, PANSS negative score, PANSS Negative Marder Factor score, and CGI-S score will be evaluated at scheduled visits.
Pharmacokinetic assessment:	Trough concentrations at scheduled visits.
Exploratory assessments	Cognition testing using CANTAB; prolactin levels; digital biomarkers of schizophrenia; EMA PRO and EMA VLMT will be evaluated during scheduled visits or on specified study days.
Statistical Methods and Planned Analyses:	Study Populations: Enrolled population: All subjects who have given informed consent for KAR-008. Safety population: All subjects who receive at least 1 dose of KarXT during the current study will be included in the safety population and will be used in the safety analysis. Modified ITT (mITT) population: All subjects who are enrolled, received at least 1 dose of KarXT during the current study, have a valid PANSS assessment at KAR-008 baseline will be included in the mITT population and will be used in the efficacy analysis.

	PK population: All subjects who have received at least 1 dose of KarXT and have at least 1 measurable plasma concentration in the current study will be included in the PK population. The primary safety endpoint of the study is the incidence of TEAEs. Secondary safety endpoints are the incidence of serious TEAEs and the incidence of TEAEs leading to withdrawal of KarXT. The secondary efficacy endpoints are change from baseline to Week 52 in the PANSS total score, PANSS positive score, PANSS negative score, PANSS Negative Marder Factor score, CGI-S score, and the percentage of PANSS responders at Week 52. The exploratory endpoints of the study are change from baseline in cognition (CANTAB), prolactin levels, digital biomarkers, EMA PRO, and EMA VLMT. Descriptive statistics will be used to provide an overview of the safety and efficacy results. For continuous parameters, descriptive statistics will include n, mean, median, standard deviation, minimum and maximum; For categorical parameters, the number and percentage of subjects in each category will be presented. The denominator for percentages will be based on the number of subjects appropriate for the purposes of analysis. No statistical hypothesis testing will be performed.

3 TABLE OF CONTENTS

3.1 List of In-text Tables

3.2 List of In-text Figures

4 LIST OF ABBREVIATIONS

Abbreviation	Definition
AD	Alzheimer's disease
AE	adverse event
AESI	adverse event of special interest
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
APD	antipsychotic drug
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{0-12}	area under the plasma concentration-time curve from 0 to 12 hours
AUC_{0-24}	area under the plasma concentration-time curve from 0 to 24 hours
BACS	Brief Assessment of Cognition in Schizophrenia
BARS	Barnes Akathisia Rating Scale
BID	twice daily
BMI	body mass index
BP	blood pressure
CANTAB	Cambridge Neuropsychological Test Automated Battery
CFR	Code of Federal Regulations
CGI-S	Clinical Global Impression–Severity
C_{max}	maximum plasma concentration
CNS	central nervous system
COVID-19	coronavirus disease 2019
C-SSRS	Columbia-Suicide Severity Rating Scale
DSM-5	Diagnostic and Statistical Manual–Fifth Edition
EDC	electronic data capture
ECG	electrocardiogram
EOS	end of study
EOT	end of treatment
ET	early termination
eCRF	electronic case report form
EMA	Ecological Momentary Assessment
EMAW	Ecological Momentary Assessment Wellness

Abbreviation	Definition
EPS	extrapyramidal symptoms
ET	early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
HIPAA	Health Insurance Portability Accountability Act
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	interactive web response system
IXRS	interactive response system
MCC	microcrystalline cellulose
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini International Neuropsychiatric Interview
mITT	modified intent-to-treat
MMRM	mixed model repeated measures
OLE	open-label extension
PANSS	Positive and Negative Syndrome Scale
PI	principal investigator
PK	pharmacokinetic(s)
PRO	patient reported outcome
SAS	Simpson-Angus Rating Scale
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Simpson Angus Scale
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TID	thrice daily
TK	toxicokinetic

Abbreviation	Definition
T_{max}	time to maximum observed plasma concentration
ULN	upper limit of normal
US	United States
VAS	visual analog scale
VLMT	Verbal Learning and Memory Test
WOCBP	women of childbearing potential

5 INTRODUCTION

5.1 Background on Schizophrenia

Schizophrenia is a long-term mental disorder involving a breakdown in the relation between thought, emotion, and behavior, and leads to faulty perception, inappropriate actions and feelings, withdrawal from reality and personal relationships into fantasy and delusion, and a sense of mental fragmentation. Symptoms include delusions, hallucination, disorganized speech or behavior, and impaired cognitive ability.[1] The prevalence of schizophrenia is between 0.6% and 1.9% in the United States population.[2] Moreover, a claims analysis has estimated that the annual prevalence of diagnosed schizophrenia in the United States (US) is 5.1 per 1000 lives.[3] It is found equally in males and females, with males usually having an earlier onset of symptoms.[4]

Antipsychotic drugs (APDs) are the mainstay of treatment for schizophrenia.[5] All currently available antipsychotics act through blockage of all or subsets of dopamine receptors in the brain. First-generation APDs include chlorpromazine and haloperidol; treatment with these agents is marked by high rates of parkinsonian extrapyramidal symptoms (EPS) and tardive dyskinesia and they consequently have limited use today. The second-generation agents, that include risperidone, olanzapine, quetiapine, lurasidone, aripiprazole, and lumateperone, tend to have lower levels of EPS or tardive dyskinesia and are currently the most commonly prescribed APD class. However, the second-generation drugs also have problematic side effects that include significant weight gain, metabolic disturbances, sedation, and akathisia.[6, 7, 8] These side effects contribute to poor medication adherence resulting in frequent relapses and hospitalizations.[9, 10] Thus, there is a need for medications for schizophrenia which act through alternative mechanisms.

Central muscarinic receptors have been hypothesized to be therapeutic treatments for schizophrenia based on several converging lines of evidence including both animal and human studies.[11, 12] There are 5 subtypes of muscarinic receptors (M1-M5). The therapeutic effect of central muscarinic receptor agonism is thought to be due to agonism of M1 and M4 receptors in the central nervous system (CNS).[13] However, compounds that agonize M1 and M4 receptors are often not specific enough not to also agonize M2 and M3 receptors outside of the CNS due to the highly conserved allosteric binding sites that the receptors share, leading to adverse events (AEs) related to activation of these peripheral receptors. Thus, any potential benefit of muscarinic agonists in schizophrenia (or other indications such as Alzheimer's disease [AD]) has been outweighed by the occurrence of AEs associated with peripheral cholinergic side effects (nausea, vomiting, diarrhea, sweating, and excess salivation).

5.2 Background on KarXT (Xanomeline Tartrate and Trospium Chloride)

Xanomeline tartrate is a muscarinic-cholinergic receptor agonist. It has agonistic activity at all 5 muscarinic receptors, but preferentially stimulates M_1 and M_4 receptors and binding to M_1 and

M_4 receptors in the CNS, which is thought to be responsible for the drug's potential therapeutic effects (Roth, unpublished data). A recent study reports that xanomeline is a very potent M_4 muscarinic agonist in vivo, measured by various second messenger assays.[14] Xanomeline also enters the brain rapidly achieving a brain to plasma ratio of greater than 10 making it an attractive CNS drug candidate.[15]

Xanomeline does not have any direct binding activity on dopaminergic receptors, suggesting that its mechanism of action is unrelated to direct dopamine involvement.

Previous double-blind, placebo-controlled clinical trials have provided strong evidence that xanomeline has clinically relevant antipsychotic efficacy. In a multicenter outpatient trial in AD (N = 343), 3 doses of xanomeline (up to 225 mg/day) and placebo were assessed for 26 weeks.[16, 17] Significant dose-dependent improvements in psychotic symptoms relative to placebo were observed. Moreover, psychotic symptoms resolved quite rapidly in subjects who were symptomatic at baseline and a dose-dependent reduction in the emergence of psychotic symptoms versus placebo was also observed. In a completer analysis, cognitive improvement was also found suggesting longer treatment intervals may be necessary for cognitive enhancement.[16, 17] In a subsequent small (N = 20) double-blind, placebo-controlled inpatient trial in treatment-resistant subjects with schizophrenia, xanomeline (225 mg/day) demonstrated robust and relatively rapid improvement in psychosis compared to placebo. In addition, improvement in both negative symptoms and cognitive impairment was observed.[18]

In both the AD and schizophrenia trials, as well as in previous healthy volunteer studies, dose-dependent "cholinergic" AEs were also reported, namely vomiting, nausea, diarrhea, sweating, and hypersalivation. These side effects were frequent and, at the higher doses of xanomeline, led to significant rates of discontinuation in the AD studies. This "cholinergic" AE profile curtailed further development of xanomeline as a single agent.

It is believed that the procholinergic AEs associated with xanomeline are mediated by xanomeline's stimulation of *peripheral* rather than *central* muscarinic receptors, which would make these AEs theoretically amenable to counteracting peripheral anticholinergic treatment. Trospium chloride is a peripherally acting muscarinic antagonist which binds to and antagonizes all 5 muscarinic receptor subtypes.[19] It is a commonly used generic drug approved for over 10 years by the US Food and Drug Administration (FDA) and by European authorities to treat overactive bladder and is generally well tolerated.[19] Several human subject studies have demonstrated that trospium does not appreciably cross the blood-brain barrier, consistent with the drug's quaternary ammonium structure.[20]

KarXT is a novel combination of xanomeline tartrate and trospium chloride. Karuna hypothesized that the addition of trospium would mitigate peripheral procholinergic side effects (vomiting, nausea, diarrhea, sweating, and hyper-salivation) and thus provide a strategy to allow xanomeline to be administered and stimulate brain muscarinic receptors with a decreased side effect burden. Phase 1 studies in healthy volunteers of this combination demonstrated that KarXT reduced these side effects by 46% compared to xanomeline alone.[21] Moreover, the

remaining cholinergic AEs were generally mild to moderate in severity and transient in nature, often lasting a few hours without recurrence and were generally single-episode. In general, KarXT was well tolerated in healthy adult volunteers. These encouraging safety data prompted further work to assess KarXT for the treatment of schizophrenia and potentially other CNS disorders.

Karuna has recently completed an adequate and well-controlled, randomized, multi-center Phase 2, placebo-controlled, inpatient clinical trial of acute psychosis with schizophrenia in 182 adult subjects (KAR-004). KarXT demonstrated a statistically significant and clinically meaningful 11.6 point mean reduction in total Positive and Negative Syndrome Scale (PANSS) at 5 weeks compared to placebo ($p < 0.0001$), with statistical separation at each time point assessed (2, 4 and 5 weeks), and also demonstrated good overall safety and tolerability.

The purpose of the current study is to evaluate the long-term safety and tolerability of KarXT (xanomeline 125 mg/trospium 30 mg) administered twice daily (BID) in adult outpatients with Diagnostic and Statistical Manual–Fifth Edition (DSM-5) diagnosis of schizophrenia.

Xanomeline is currently not approved or marketed in any country. Trospium is marketed in the US and other regions of the world for the treatment of overactive bladder.

5.2.1 Nonclinical Studies

The following is a summary of the important nonclinical safety and toxicology studies. More detailed information can be found in the KarXT Investigator's Brochure (IB).

The acute toxicity of xanomeline tartrate was evaluated in mice and rats. All animals were observed for 2 weeks for mortality and clinical signs of intolerance, and then necropsied for gross examinations. In-life findings attributed to the test article included excessive muscarinic-mediated pharmacology, such as excessive salivation, hypoactivity, ataxia, soft stools, exophthalmos, ocular discharge, tremors, and convulsions, with survivors typically appearing normal by Day 3 or Day 4. Gross findings at necropsy were generally unremarkable (eg, gas-distended or mucous-filled gastrointestinal [GI] tracts after oral dosing).

KarXT-301 was a 14-day, repeat dose study of KarXT in rats where relatively high doses of xanomeline and trospium were given, with either xanomeline alone or in combination with trospium. Seven groups of 10 rats/sex/group were administered either vehicle (reverse osmosis water), xanomeline alone at 37, 75, 150, or 300 mg/kg/day (split into BID doses, every 12 hours), or xanomeline/trospium combination doses of 150/200 mg/kg/day or 225/400 mg/kg/day, respectively (split into BID doses, every 12 hours).

Satellite animals were included for the collection of plasma after the first and last doses for the determination of drug concentrations of each parent drug in support of toxicokinetic (TK) assessments.

There was no target-organ toxicity revealed by clinical pathology or by gross or microscopic assessments. All intolerance could be attributed to recognized pharmacology of either test article.

No dose-related ophthalmic observations were noted. Findings were not indicative of specific target organ toxicity. In short, no new hazard was identified.

Clinical observations noted in most animals administered 300 mg/kg/day xanomeline included hypoactivity, clear oral discharge, dilated pupils, irregular or labored respiration, and rough haircoat, among other observations. These findings are generally consistent with the anticipated pharmacology of xanomeline.

Three TK animals in the low-dose combination group died or were euthanized in extremis. It is unclear to what extent the combination treatment effects versus the different handling of these animals (including 3 plasma samplings per animal) contributed to these deaths. If gavage accidents were involved (as happened with some TK animals), then they were not detected at gross necropsy. There was no microscopic evidence of toxicity seen in any toxicity animals in this group or in the higher-dose combination group.

Three toxicology and 3 TK animal deaths (total of 6) occurred in the high-dose combination group. Two toxicology animals had evidence of gavage accidents. For the third, the cause of death was undetermined, and a test article-related effect cannot be ruled out, but esophageal muscular degeneration/regeneration is indicated in some dosing-related trauma. If gavage accidents were involved, then they were not detected at gross necropsy. There was no evidence of target organ microscopic findings in GI tract or any other tissue of any animal, including the early death toxicity animals.

A pharmacodynamics (PD)-mediated reduction in GI motility is consistent with the anti-muscarinic effects of trospium on intestinal musculature. Fecal retention, malabsorption, cessation of eating, dehydration, and rapid deterioration followed with continued dosing. Cessation of dosing in the high-dose combination animals that survived led to rapid recovery, implying the deleterious effects had been PD-related. No effects on food consumption were seen in any xanomeline-alone group. The lack of microscopic findings in the GI tract of any early death or surviving animal implies that the adverse effects were pharmacologically mediated rather than direct target organ toxicity.

Twenty-eight Day Repeat-Dose Studies with Xanomeline in Rats and Monkeys: Rats were fed xanomeline tartrate at 0, 0.05, 0.1, or 0.2% daily and monkeys were fed xanomeline tartrate daily at 0, 5, 12.5, or 30 mg/kg. All animals survived until necropsy. Safety findings in rats included reduced body weight in the high-dose group, increases in gamma-glutamyl-transferase, cholesterol, and bilirubin, slight decreases in triglycerides, bile duct hyperplasia, higher serum potassium (males), and lower serum globulin (females). Findings in monkeys were dose-related and included signs of intolerance such as emesis, salivation, diarrhea, hypoactivity, weight loss, and treatment-related tachycardia in the high-dose animals.

Forty-Day Repeat Dose Study of KarXT in Rats (KarXT-302): Six groups of 15 rats/sex/group were given vehicle, xanomeline alone at 75 or 150 mg/kg/day, trospium alone at 100 mg/kg/day, or xanomeline/trospium combination at doses of 75/50 mg/kg/day or 150/100 mg/kg/day, with

all doses split into BID doses. Satellite rats (TK animals) were included for collection of plasma after the first and last doses to determine concentrations of each drug. Dosing was initially planned to be 90 days, but was terminated after 40 days because of unexpected deaths in the TK animals. No target organ toxicity was seen. Safety findings included pharmacologically mediated constipation in the trospium alone and combination groups, and mild biliary hyperplasia in the high-dose xanomeline-alone and combination groups. There were 4 unscheduled deaths in TK animals; 2 in the high-dose xanomeline-alone group (150 g/kg/day) and 2 in the high-dose combination group (150 mg/kg/day xanomeline plus 100 mg/kg/day trospium). Both xanomeline-only animals had necropsy gross findings of a gavage accident and cause of death could not be determined. All toxicology animals survived to their scheduled sacrifice. The Sponsor considers that the volume depletion and trauma of multiple bleeds (3 per animal) followed by reduced absorption of fluids and nutrients secondary to reduced GI motility with continued BID dosing, explains the greater demise of TK animals relative to toxicity animals.

Based on the results of the 90-day rat toxicology study, oral administration of trospium chloride and xanomeline tartrate alone or in combination to Crl:CD(SD) rats BID (12 hours ±60 minutes apart) at dosage levels of 25 and 50 mg/kg/dose trospium chloride, 37 and 75 mg/kg/dose xanomeline tartrate and a combination of 37/25, 75/25, and 75/50 mg/kg/dose xanomeline tartrate/trospium chloride for a minimum of 90 days resulted in minimal to moderate bile duct hyperplasia in the livers of the xanomeline tartrate and combination (xanomeline tartrate and trospium chloride) group males.

Although there were no notable differences in the incidence of bile duct hyperplasia when comparing the single vs combination groups, there was an increased severity observed in the combination group males (specifically the 75/25 and 75/50 mg/kg/dose combination group males) when compared to the xanomeline tartrate group males at the terminal euthanasia. The bile duct hyperplasia was considered adverse in the high-dose xanomeline tartrate group males and in the 75/25 and 75/50 mg/kg/dose combination group males due to instances of moderate severity. Therefore, the no-observed-adverse-effect level was considered to be 50 mg/kg/dose for trospium chloride, 37 mg/kg/dose for xanomeline tartrate, and 37/25 mg/kg/dose for the combination of xanomeline tartrate/trospium chloride. At these doses for males, mean plasma AUC_{0-24} values were 27,700 pg•hr/mL for trospium, 146,000 pg•hr/mL for xanomeline, and 4510 + 111,000 pg•hr/mL for trospium + xanomeline, respectively, on Day 91.

At these doses for females, mean plasma AUC_{0-24} values were 9230 pg•hr/mL for trospium, 267,000 pg•hr/mL for xanomeline, and 16,700 + 171,000 pg•hr/mL for trospium + xanomeline, respectively, on Day 91. The absence of bile duct hyperplasia in females cannot be explained from differences in drug exposure. At the recovery euthanasia, bile duct hyperplasia was still present, but was limited to minimal severity and there was a decreased incidence in both the xanomeline tartrate and combination group males. There was also no notable difference in severity between the single vs combination groups at the recovery euthanasia. Given the decreased incidence/severity, in combination with the improved histologic appearance of bile

ducts at the recovery euthanasia (ie, smaller/flattened epithelium, non-inflammatory, and an absence of portal bridging), changes at the recovery euthanasia were consistent with a partial resolution of bile duct hyperplasia. With an absence of correlating serum liver enzyme elevations, bile acid alterations or hepatocellular degeneration, necrosis or regeneration, and with the apparent reversibility following cessation of treatment, these findings appear to have been tolerable by the affected animals. Therefore, the maximum tolerated dose was considered to be 50 mg/kg/dose for trospium chloride, 75 mg/kg/dose for xanomeline tartrate, and 75/50 mg/kg/dose for the combination of xanomeline tartrate/trospium chloride.

For males, corresponding mean plasma AUC_{0-24} values were 27,700 pg•hr/mL for trospium, 822,000 pg•hr/mL for xanomeline, and 133,000 + 276,000 pg•hr/mL for trospium + xanomeline, respectively, on Day 91. For females, corresponding mean plasma AUC_{0-24} values were 9230 pg•hr/mL for trospium, 2,090,000 pg•hr/mL for xanomeline, and 17,600 + 950,000 pg•hr/mL for trospium + xanomeline, respectively, on Day 91.

In summary, no new "combination" findings were discovered; toxicology studies revealed the familiar exaggerations of systemic and CNS muscarinic effects that had previously been seen with xanomeline or trospium at high doses. Target organ findings with xanomeline alone were limited to biliary hyperplasia in the 28-day rat study but not the 28-day or 12-month monkey study, though similar findings were described in a 6-month monkey study. With KarXT, biliary hyperplasia was not observed in the 14-day rat study but was reported in the 40-day rat study. Notably, these hyperplastic findings are not thought to represent pre-neoplastic lesions, because they were of low severity; no fibrosis or associated hepatocellular changes, and no significant effects were seen on hepatobiliary-related serum chemistry.

5.2.2 Completed Clinical Studies

Refer to the IB for complete information regarding previous clinical studies conducted with xanomeline by Eli Lilly, and studies KAR-001, KAR-002, KAR-003 and KAR-004 conducted by Karuna Therapeutics using xanomeline with trospium.

To date, more than 840 subjects or volunteers have been exposed to xanomeline tartrate (oral formulation, either alone, in combination with trospium, or as the combination drug KarXT) in 19 completed clinical studies conducted either by Eli Lilly or Karuna Therapeutics, some for as long as 3 years. In those studies, significant improvements in cognition and reduced psychotic symptoms were observed.

A study of xanomeline monotherapy in subjects with schizophrenia was reported in 2008.[18] In this pilot study, the effects of xanomeline were examined in 20 schizophrenia subjects utilizing a double-blind, placebo-controlled, 4-week study design. Subjects treated with xanomeline did significantly better than subjects in the placebo group on Brief Psychiatric Rating Scale total scores and PANSS total scores (ie, 24-point change over placebo, $p = 0.04$). In the cognitive test battery, subjects in the xanomeline group showed improvements relative to placebo in some of the cognitive domains of verbal learning and short-term memory function. These studies

demonstrated the potential for xanomeline as a treatment for psychosis and cognition across multiple subject populations.

Study H2Q-EW-E001, conducted by Eli Lilly, had 36 male healthy volunteers in 4 groups of 9, who were administered escalating single doses of xanomeline tartrate in increments of 1, 5, 10, 25, 50, 75, 100 and 150 mg. Each group took 2 ascending doses of xanomeline tartrate and 1 dose of placebo in a single subject blind manner. There were no serious AEs (SAEs). Adverse events included watery diarrhea, nausea, dizziness, sweating, shivering, mild disorientation, increased blood pressure (BP), increase(s) in sitting and standing heart rate, slight increase in supine systolic BP, and postural hypotension.

The clinical experience with KarXT initiated by Karuna Therapeutics to date includes 3 completed Phase 1, clinical pharmacology studies in healthy volunteers (KAR-001, KAR-002, and KAR-003) and one completed Phase 2 study (KAR-004) in adult inpatients with DSM-5 schizophrenia.

The first study conducted by Karuna, KAR-001 was a Phase 1, double-blind, randomized, multiple-dose, pilot study comparing xanomeline administered alone to xanomeline administered in combination with trospium chloride in normal healthy volunteers. This study consisted of 2 arms, in which xanomeline was administered three times daily (TID), alone, at a total daily dose of 225 mg in 1 arm, and the second arm received the same dose of xanomeline in combination with trospium chloride 20 mg administered BID, a total daily dose of 40 mg. Subjects were treated for 7 days. The goal was to determine whether this dosing regimen would reduce the cholinergic side effects of xanomeline by co-administration of the muscarinic antagonist, trospium.

Overall, treatment with xanomeline 225 mg daily + trospium 40 mg daily administered over 7 days was considered safe and well tolerated. The results of key and supportive endpoints showed a numerical reduction (although not statistically significant) in visual analog scale (VAS) scores for cholinergic events for the xanomeline + trospium treatment arm compared to the xanomeline-alone treatment arm. Specifically, consistent numerical reduction in VAS scores for the xanomeline + trospium treatment arm was observed for the supportive endpoints of maximum weekly individual VAS scores and mean daily maximum composite VAS scores.

Results of the clinician-administered scales were supportive of a reduction in vomiting, feelings of nausea, excess salivation, and sweating that interfered with daily activities in the xanomeline + trospium treatment arm compared to the xanomeline-alone treatment arm.

There were no meaningful differences between treatment groups in heart rate, resting BP, orthostatic BP or any electrocardiogram (ECG) parameters including QT. A small subset of subjects in both treatment arms had transient increases in heart rate and orthostatic BP changes which may have contributed to syncope and postural dizziness in those subjects. Two subjects (both in the xanomeline-alone arm) experienced syncope. The incidence of orthostatic AEs in the KarXT group was approximately one-half that of subjects in the xanomeline-alone group.

The most commonly reported treatment-emergent AEs (TEAEs) in KAR-001 (≥20% of subjects in either treatment arm) were hyperhidrosis, salivary hypersecretion, nausea, dizziness postural, and diarrhea. Subject incidences of these 5 TEAEs was higher in the xanomeline-alone treatment arm (61.8%) compared to the xanomeline + trospium treatment arm (34.3%).

Overall, treatment with xanomeline 225 mg combined with trospium chloride 40 mg administered over 7 days was considered safe and well tolerated. The observed side effect profile was consistent with the known safety profile of xanomeline and trospium chloride. The incidence of TEAEs and cholinergic TEAEs was lower in the xanomeline + trospium treatment arm compared to the xanomeline-alone treatment arm.

Study KAR-002 was a Phase 1, double-blind, randomized, multiple-dose adaptive design pilot study to evaluate the safety and tolerability of KarXT in normal healthy volunteers. Subjects received either 100 mg xanomeline + 20 mg trospium BID or placebo. The first cohort of this study was stopped after 1.5 days when the FDA put the program on hold due to a preliminary rat finding in the 14-day study. This study used a new formulation of KarXT in which xanomeline and trospium were combined into a single dose form and given BID. Safety findings included an increase in orthostatic complaints. Caution should be used in drawing conclusions from this study, as subjects did not have time to reach steady state plasma levels from dosing, as only 3 doses were given.

Study KAR-003 was a Phase 1, double-blind, randomized, multiple-dose, adaptive design, inpatient pilot study to evaluate the safety and tolerability of KarXT in normal healthy volunteers. The primary objective of this study was to assess the safety and tolerability of 7 days of daily administration of KarXT at various dose combinations, administered BID. Subjects received either KarXT or placebo (3:1 ratio). All subjects on KarXT received 2 days of 50 mg xanomeline + 20 mg trospium BID, and then increased to different doses for Days 3 to 7. This study also used the new formulation of KarXT in which xanomeline and trospium were combined into a single dosage form and given BID.

There was a relatively high degree of variability in xanomeline and trospium exposures between individuals in all cohorts, which is consistent with previous results with KarXT, xanomeline-alone, and trospium-alone. Peak plasma concentrations were observed at a median time of 2.0 hours for xanomeline and 1.0 hour for trospium across all treatment groups and study days.

Although there was insufficient data to draw a definitive conclusion regarding the impact of trospium on the pharmacokinetics (PK) and bioavailability of xanomeline, or the impact of xanomeline on the pharmacokinetics and bioavailability of trospium, the PK results suggest that neither drug had a meaningful impact on the PK behavior of the other drug.

During the 2-day lead-in phase, the most common AEs (≥20% of subjects) when all the subjects completed dosing were dry mouth, nausea, and constipation. For the treatment groups that completed dosing, although the incidence of TEAEs was lower in the KarXT 100/20 BID

(66.7%) group compared to KarXT 125/40 group (88.9%), the incidence of cholinergic TEAEs (nausea, vomiting, diarrhea, sweating, and excess salivation) was similar between the 2 groups. The most commonly reported TEAEs (≥20% of subjects in either treatment group) in these groups were dizziness, nausea, dry mouth, headache, vomiting, dyspepsia, somnolence, vision blurred, and dysuria. For the treatment groups that did not complete dosing (KarXT 150/20 BID group and KarXT 150/40 BID group), the cholinergic TEAEs were generally higher compared to the treatment groups that completed dosing.

Overall, anticholinergic TEAEs appeared to occur primarily in the treatment groups that were dosed with 40 mg trospium BID (KarXT 150/40 BID and KarXT 125/40 BID groups), particularly when paired with 125 mg xanomeline BID, suggesting to consider slightly lowering the trospium dose from 40 mg BID in future studies. All TEAEs were mild or moderate in severity, and there were no SAEs or deaths. Treatment-emergent AEs were primarily cholinergic or orthostatic (and a few anticholinergic). Doses of 100 mg and 125 mg BID of xanomeline were well tolerated when paired with 20 mg and 40 mg BID of trospium, respectively. The safety and tolerability profile of KarXT 100/20 BID and KarXT 125/40 BID was acceptable and supports further evaluation at similar doses in future studies. Doses of KarXT 150/20 BID and 150/40 BID were not well tolerated in this study. A pairing of 150 mg xanomeline with 40 mg trospium appeared to be better tolerated than 150/20, but some subjects still experienced tolerability issues.

Study KAR-004 was a Phase 2 randomized, double-blinded study to assess the safety, tolerability, and efficacy of KarXT in adults with DSM-5 schizophrenia, hospitalized with acute psychosis. The primary objective of the study was to assess the efficacy of KarXT (125/30 BID) versus placebo in reducing PANSS total scores in adult inpatients with a DSM-5 diagnosis of schizophrenia. Subjects received either KarXT or placebo (1:1 ratio) for a treatment period of 5 weeks. All subjects on KarXT received a lead-in dose of KarXT 50/20 BID for the first 2 days followed by KarXT 100/20 BID on Days 3 to 7. On Day 8, dosing was titrated upwards to KarXT 125/30 BID unless the subject was continuing to experience AEs from a previous dose increase of 100/20 BID.

A total of 182 subjects were enrolled and randomized (92 placebo; 90 KarXT). Of these subjects, 170 (87 [94.6%] placebo; 83 [92.2%] KarXT) received at least one dose of study drug and had at least one post-baseline PANSS assessment (Modified Intent to Treat population used for the efficacy analyses). Discontinuation rates were similar between the 2 treatment groups; 37 subjects discontinued the study early (19 [20.7%] placebo; 18 [20.0%] KarXT). The most common reason for early discontinuation was consent withdrawn (14 [15.2%] placebo; 14 [15.6%] KarXT) followed by Adverse Event (2 [2.2%] placebo; 3 [3.3%] KarXT).

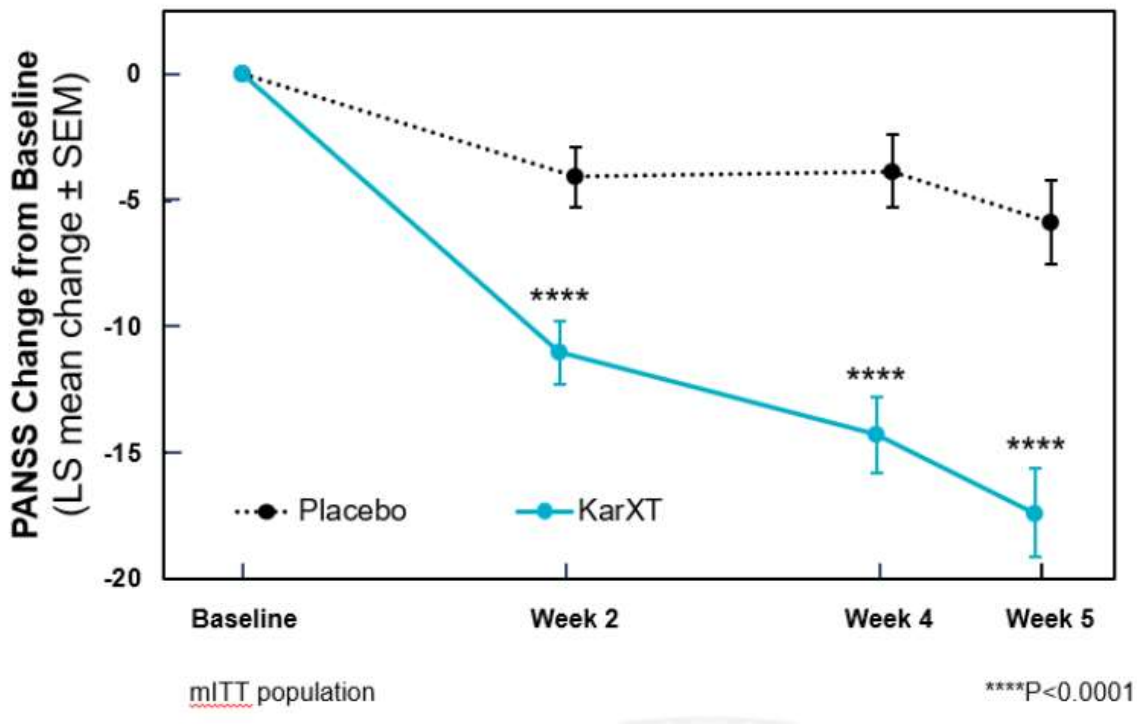
Treatment-emergent adverse events (TEAE) were reported in 43.3% of subjects in the placebo group and 53.9% of subjects in the KarXT group. The most commonly reported TEAEs were constipation, nausea, dry mouth, dyspepsia, and vomiting, and were more common (≥ 5% higher or twice that of placebo) in the KarXT group than in the placebo group.

There were 27.8% and 42.7% of subjects in the placebo and KarXT groups, respectively, who experienced at least 1 TEAE related to study drug. The most commonly reported study drug related TEAEs for the placebo and KarXT total groups were nausea, constipation, dry mouth, dyspepsia, and vomiting and were more common (≥ 5% higher or twice that of placebo) in the KarXT group than in the placebo group. The majority of the reported TEAEs were mild (27.8% placebo; 36.0% KarXT) or moderate (14.4% placebo; 16.9% KarXT) in severity. Two severe TEAEs were reported during the study. One subject in the placebo group had a severe TEAE of worsening schizophrenia symptoms, and 1 subject in the KarXT high dose group had a severe event of increased psychosis which was reported as an SAE possibly related to KarXT by the investigator. There were no other SAEs reported during the study and there were no deaths during the study.

The pattern and course of safety findings in KAR-004 were consistent with the known safety profile from earlier studies of both xanomeline monotherapy and xanomeline combined with trospium (KarXT). Even though the qualitative AE profile was consistent with earlier Phase 1 PK/safety studies in healthy volunteers, the relative tolerability burden was lower in the current study of schizophrenia patients receiving KarXT than in the healthy volunteers. In addition, the safety and tolerability of KarXT was favorable and notably free of many common side effects associated with current antipsychotic drugs.

KarXT demonstrated statistically significant and clinically meaningful reduction in total PANSS score at all time points over 5 weeks compared to placebo (Figure 1). The primary efficacy endpoint result for the study (change from baseline (CFB) in PANSS total score between the placebo group and the KarXT group at Visit 9/Week 5) showed a statistically significant decrease in PANSS total score ($p<0.0001$). The statistically significant difference in CFB between the treatment groups was there at Visit 6/Week 2 ($p<0.0001$) and continued to Visit 8/Week 4 and Visit 9/Week 5. Overall, the decrease from baseline in PANSS total score for the KarXT group was statistically significantly greater compared to the placebo group by treatment group for Visits 6, 8, and 9 ($p<0.0001$).

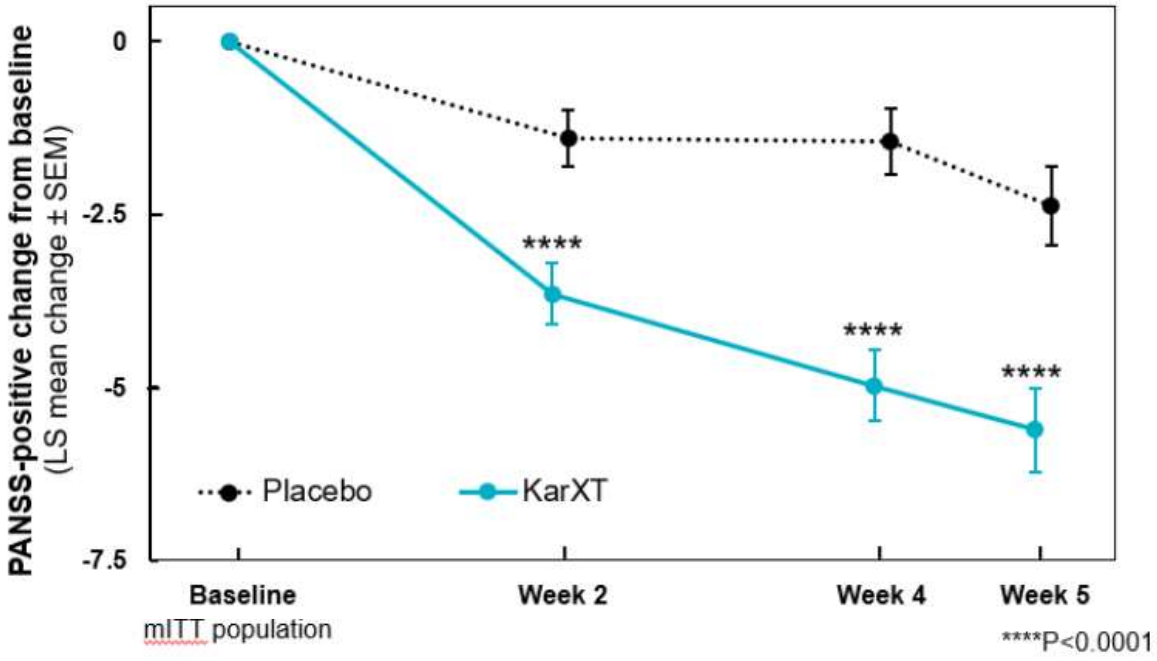
Figure 1. Change from Baseline in PANSS Total Scores (KAR-004)



Abbreviations: LS = least squares; mITT = modified intent-to-treat; PANSS = Positive and Negative Syndrome Scale; SEM = standard error of the mean.

A significant reduction in the secondary endpoint of PANSS-positive scores was observed ($p<0.0001$) at Week 5 as well as the 2 earlier time points (ie, Weeks 2 and 4; see Figure 2).

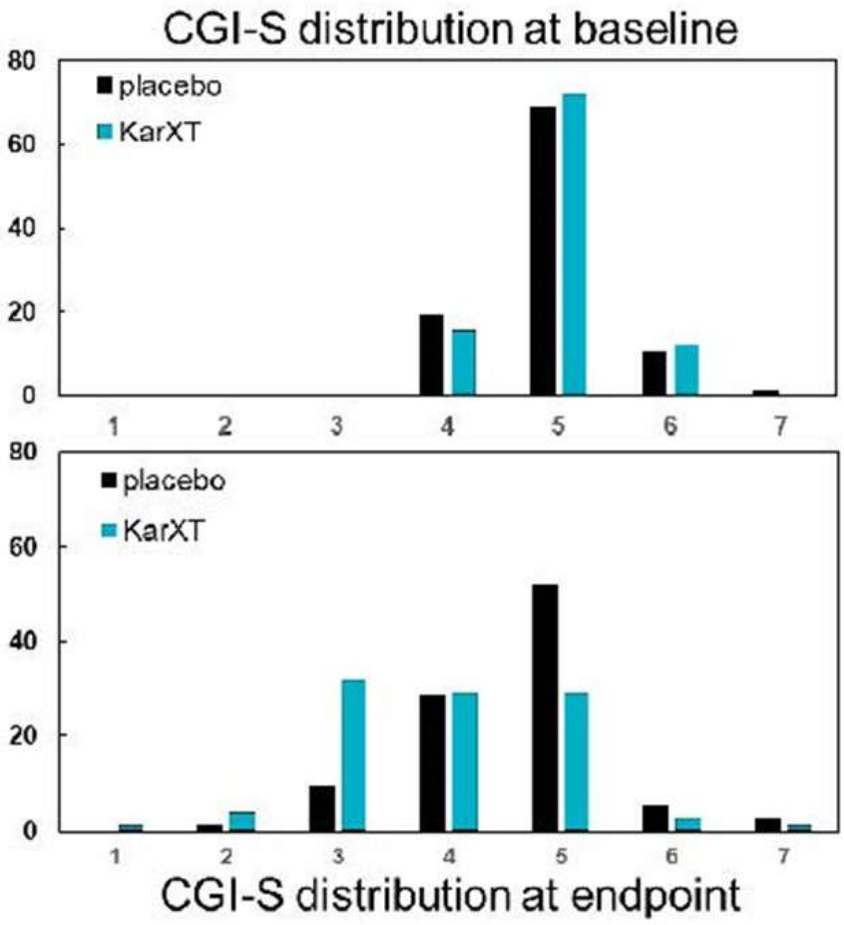
Figure 2. Change from Baseline in PANSS-Positive Scores (KAR-004)



Abbreviations: LS = least squares; mITT = modified intent-to-treat; PANSS = Positive and Negative Syndrome Scale; SEM = standard error of the mean.

As regards the Clinical Global Impression – Severity of Illness (CGI-S), subjects in the KarXT group overall significantly improved in ratings compared to placebo, with a p-value of <0.001 at Week 5. At Week 5, 8% of placebo subjects improved (decreased) their CGI-S ratings at least 2 levels versus 28.9% of KarXT subjects (see Figure 3).

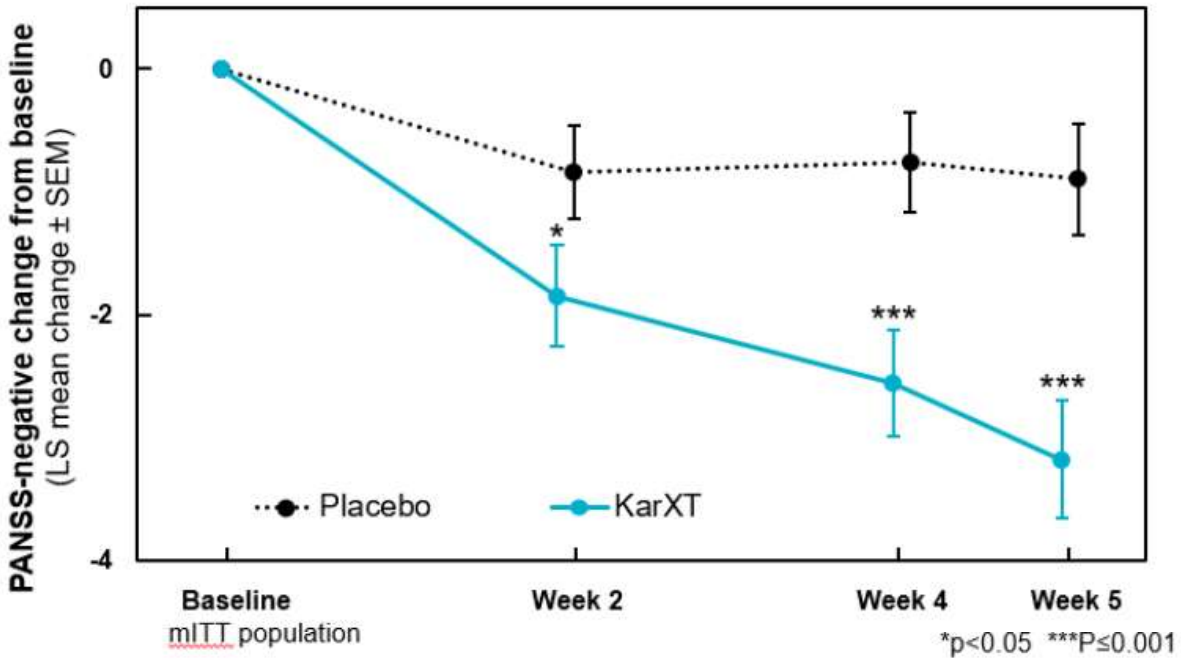
Figure 3. Change from Baseline in CGI-S (KAR-004)



Abbreviation: CGI-S = Clinical Global Impression–Severity.

A statistically significant reduction in the secondary endpoint of PANSS-negative score was observed ($p<0.001$) at Week 5. Overall, the changes in the KarXT group were statistically significantly greater compared to the placebo group at Visits 6, 8, and 9 ($p<0.001$). The least square mean improvement for the placebo group was 1.32 points at Week 5 (Visit 9) and the mean improvement for the KarXT group was 3.85 points leading to a mean difference of 2.53 points at Week 5 (Visit 9; see Figure 4).

Figure 4. Change from Baseline in PANSS-Negative Scores (KAR-004)



Abbreviations: LS = least squares; mITT = modified intent-to-treat; PANSS = Positive and Negative Syndrome Scale; SEM = standard error of the mean.

The overall safety/tolerability data were also fairly unambiguous; among the highlights:

- The overall discontinuation rate on KarXT was 20%, similar to placebo (21%). The number of discontinuations due to TEAEs was equal in the KarXT and placebo arms (N = 2 in each group)
- The dose escalation rate on KarXT was high and similar to placebo:
  - 91% of KarXT subjects escalated to 125/30 KarXT (vs 97% on placebo)
  - 4% percent de-escalated back to 100/20 KarXT dose (vs 1% on placebo)
- The overall TEAE rate on KarXT was 54% vs 43% on placebo:
  - The most common TEAEs were constipation, nausea, dry mouth, dyspepsia, and vomiting. None of these TEAEs were severe and none led to discontinuations
  - One SAE occurred in the study (the subject was on KarXT): the subject discontinued treatment and subsequently sought hospital care for worsening psychosis, meeting the regulatory definition of an SAE.
  - No syncope or mean changes in BP were seen

- A 5.5 bpm peak mean placebo adjusted resting heart rate increase with a downward trend after Week 2 was seen
- One subject (on KarXT) was discontinued due to an elevated gamma-glutamyl transpeptidase (GGT)
- There were no new safety findings associated with KarXT that have not been observed with either xanomeline alone or trospium alone in previous trials

- KarXT did not show evidence of many of the kinds of AEs that often occur in currently available antipsychotics for the treatment of schizophrenia
- The rates of the following AEs were similar for KarXT and placebo: somnolence, weight gain, and EPS
- Overall, the KAR-004 results confirm and extend the antipsychotic benefit of xanomeline observed in past studies of xanomeline alone and the well tolerated nature of KarXT. KAR-004 results support the continued development of KarXT into Phase 3 trials.

Two randomized, double-blind, placebo-controlled Phase 3 trials (KAR-007 and KAR-009) are planned in which the subjects will be exposed to either KarXT or placebo (1:1) for a period of up to 5 weeks. Subjects who complete either of these 2 studies will be eligible to roll over into this long-term open-label study.

5.3 Clinical Risks/Benefits of KarXT and Study Rationale

The risks and benefits of KarXT in humans are not fully known. KarXT is a fixed dose combination of xanomeline and trospium.

The available clinical trial data indicate that KarXT has robust efficacy and a favorable safety profile that appears unique compared to all available APDs. Most of these clinical data were generated by subjects who were either “institutionalized” or studied in an “inpatient” hospital setting. Treatment with KarXT is not associated with weight gain, sedation, or meaningful EPS changes. In contrast, these serious side-effects pose a significant risk with other APD treatments for schizophrenia and can lead to discontinuation of treatment and significant morbidity. A Phase 2 registration quality pivotal trial in 182 subjects met the primary endpoint with the PANSS total score showing a 11.6 point mean improvement compared to placebo with a highly significant ($p < 0.0001$) separation from placebo (-17.4 KarXT vs. -5.9 placebo) at Week 5. KarXT, as compared to placebo, demonstrated highly significant reduction in PANSS total scores ($p < 0.0001$) at all post randomization time points (Weeks 2, 4 and, 5) with a calculated effects size (Cohen’s d) of 0.75. KarXT, as compared to placebo, demonstrated significant improvement at all post randomization time points for PANSS positive symptom subscores, PANSS negative symptom subscores, PANSS Marder Factor negative symptom subscores, and CGI-S scores.

Over 840 subjects or volunteers have been exposed to xanomeline tartrate (oral formulation; either alone, in combination with trospium, or as the combination drug KarXT) in clinical studies. These early clinical studies, as well as nonclinical pharmacology and toxicology studies, have not revealed any specific contraindications to the use of xanomeline. The most common side effects/symptoms are the cholinergic related effects: nausea, vomiting, excess salivation, excess sweating, and diarrhea. In addition, subjects treated with xanomeline alone have reported both syncope and orthostatic dizziness. The addition of trospium decreases the peripheral cholinergic effect of xanomeline creating a better tolerated therapy. In addition, a titration phase also increases the tolerability of KarXT.

Trospium chloride has been marketed in the US for 12 years. The most frequently reported AEs reported in pivotal trials were dry mouth, constipation, abdominal pain, headache, urinary retention, and abnormal vision and accommodation. For additional information, the package insert for trospium chloride tablets for oral use can be found in the IB.

In a Phase 2 (KAR-004) clinical study, KarXT (100/20 and 125/30) significantly reduced the symptoms of schizophrenia in subjects with acute psychosis after treatment for 28 days. KarXT also showed an acceptable safety profile with the most common TEAEs being constipation, nausea, dry mouth, dyspepsia, and vomiting. All the reported TEAEs were mild or moderate in intensity. One SAE (psychotic disorder) was reported by a single subject and no deaths were reported in the study. KarXT was generally well-tolerated and found to be safe in this patient population.

KarXT represents a novel approach to the treatment of patients with schizophrenia that will provide an important and meaningful alternative to current therapies. The current tolerability and AE profile and the efficacy of KarXT justify further development of KarXT in this patient population by advancing to Phase 3 trials. Two such Phase 3 trials (KAR-007 and KAR-009) are planned where the subjects will receive the study drug (KarXT or placebo) for 5 weeks.

In the current study, regardless of treatment assignment in the preceding Phase 3 study (KAR-007 or KAR-009), all subjects will receive KarXT for a period of approximately 52 weeks with the primary objective of assessing the long-term safety and tolerability profile of KarXT in an out-patient setting. All subjects will start with a lead-in dose of KarXT 50/20 BID for Days 1 to 2 and then the dose will be titrated to 100/20 BID for Days 3 to 7, allowing the subject to adjust to KarXT before receiving a higher dose of 125/30 BID starting on Visit 3 (Day 8), unless the subject is continuing to experience AEs from the previous dose increase of KarXT 100/20 BID. All subjects who are increased to KarXT 125/30 BID, depending on tolerability, will have the option to return to KarXT 100/20 BID. Re-escalation to 125/30 BID or re-titration in cases where subject has been off KarXT for a longer period of time (at least a week) is allowed and will require a discussion between the principal investigator (PI) and the medical monitor.

Dosing will occur every 12 ±4.5 hours each day, during waking hours. KarXT should be dosed on an empty stomach (ie, at least 1 hour before a meal or 2 to 3 hours after a meal).

The current study is designed to demonstrate that long-term treatment with KarXT in adult schizophrenia subjects is safe and tolerable.

6 STUDY OBJECTIVES AND ENDPOINTS

6.1 Study Objectives

6.1.1 Primary Objective

The primary objective of the study is to assess the long-term safety and tolerability of KarXT in subjects with a DSM-5 diagnosis of schizophrenia.

6.1.2 Secondary Objective

The secondary objective of this study is to assess the long-term efficacy and monitor trough concentrations of xanomeline and trospium after administration of KarXT in adults with a DSM-5 diagnosis of schizophrenia:

- To evaluate the reduction in PANSS total score
- To evaluate the reduction of PANSS positive score
- To evaluate the improvement in Clinical Global Impression Severity (CGI-S) results
- To evaluate the reduction of PANSS negative score
- To evaluate the reduction of PANSS Marder Factor negative symptoms score
- To measure trough concentrations of xanomeline and trospium after administration of KarXT in adults who are acutely psychotic with a DSM-5 diagnosis of schizophrenia

6.1.3 Exploratory Objectives

The exploratory objectives of this study are:

- To evaluate cognition with the Cambridge Neuropsychological Test Automated Battery (CANTAB)
- To evaluate prolactin levels after administration of KarXT
- To evaluate digital biomarkers of schizophrenia (US only)
- To evaluate ecological momentary assessment administered patient reported outcomes (EMA PRO) in schizophrenia (US only)
- To evaluate cognitive insight using an EMA administered verbal learning and memory test (EMA VLMT) in schizophrenia (US only)

6.2 Study Endpoints

6.2.1 Primary Safety Endpoint

The primary safety endpoint of this study is the incidence of treatment-emergent AEs (TEAE).

6.2.2 Secondary Endpoints

6.2.2.1 Safety Endpoints

The secondary safety endpoints of this study are:

- Incidence of serious TEAEs
- Incidence of TEAEs leading to withdrawal

6.2.2.2 Efficacy Endpoints

The secondary efficacy endpoints of this study are:

- Change from baseline in PANSS total score at Week 52
- Change from baseline in PANSS positive score at Week 52
- Change from baseline in PANSS negative score at Week 52
- Change from baseline in PANSS Negative Marder Factor score at Week 52
- Change from baseline in CGI-S score at Week 52
- Percentage of PANSS responders (a 30% change in PANSS total score) at Week 52

6.2.3 Other Endpoints

6.2.3.1 Safety Endpoints

- Spontaneously reported adverse events of special interest (AESIs)
- Spontaneously reported procholinergic and anticholinergic symptoms
- Change from baseline in Simpson-Angus Rating Scale (SAS)
- Change from baseline in Barnes Rating Scale for Akathisia (BARS)
- Change from baseline in Abnormal Involuntary Movement Scale (AIMS)
- Change from baseline in body weight, body mass index (BMI), waist circumference
- Change from baseline in orthostatic vital signs (supine and standing after 2 minutes): BP (systolic and diastolic) and heart rate
- Change from baseline in clinical laboratory assessments (hematology, clinical chemistry, coagulation, urinalysis, and drug screen)
- Change from baseline in 12-lead ECG
- Change from baseline in physical examination
- Suicidal ideation scale with the use of Columbia-Suicide Severity Rating Scale (C-SSRS)

6.2.3.2 Pharmacokinetic Endpoint

The PK endpoint of this study is measurement of trough plasma concentrations of xanomeline and trospium.

6.2.3.3 Exploratory Endpoints

The exploratory endpoints of this study are:

- Change from baseline in cognition measuring core domains of impairment in schizophrenia using CANTAB
- Change from baseline in prolactin levels
- Observed digital biomarkers of schizophrenia (US only)
- Observed ecological momentary assessment administered patient reported outcomes (EMA PRO) in schizophrenia (US only)
- Observed cognitive insight using an EMA administered verbal learning and memory test (EMA VLMT) in schizophrenia (US only)

7 INVESTIGATIONAL PLAN

7.1 Description of Overall Study Design and Plan

This is a Phase 3 multicenter, 53-week, outpatient, open-label extension (OLE) study to evaluate the long-term safety, tolerability, and efficacy of KarXT in subjects with DSM-5 schizophrenia who previously completed the treatment period of one of the two Phase 3 double-blind studies, KAR-007 or KAR-009. The study consists of a 52-week OLE treatment phase and a 7-day (±3 days) follow-up/end-of-study (EOS) visit after the last KarXT dose for subjects who complete the treatment phase and those who prematurely discontinue from the study.

After written informed consent, subjects who have completed either the KAR-007 or KAR-009 Phase 3 acute study and received the last dose of the study drug in that trial will be rolled over into the current OLE study. The assessments performed on Visit 10 (Day 35) of Studies KAR-007 or KAR-009 will be considered as baseline assessments along with any additional procedures that will be performed on Day 0 of the current study. Any scheduled Day 0 assessments that were not completed on Day 35 of the acute study (KAR-007 or KAR-009) must be completed on Day 0 of the current study.

Day 0 of the current study should be completed on the same day as Day 35 of the acute study after all Visit 10 (Day 35) procedures of the prior study KAR-007 or KAR-009 have been completed.

Subjects who did not complete the full treatment period, or who early terminated studies KAR-007 or KAR-009, will not be eligible to enroll in this long-term extension study.

A total of up to 350 subjects are planned to be enrolled in this study (aged 18 to 65 years at time of enrollment into the preceding acute study) across approximately 30 study sites in the United States and 10 study sites in Ukraine.

In this OLE study, all subjects will receive KarXT for up to 52 weeks. Regardless of treatment assignment in the preceding Phase 3 acute study (KAR-007 or KAR-009), all subjects will start on a lead-in dose of KarXT 50/20 BID for the first 2 days (Days 1 and 2), followed by KarXT 100/20 BID for the remainder of Week 1 (Days 3 to 7). On Visit 3 (Day 8), dosing will be titrated upwards to KarXT 125/30 BID unless the subject is continuing to experience AEs from the previous dose of KarXT 100/20 BID. All subjects who are increased to KarXT 125/30 BID, depending on tolerability, will have the option to return to KarXT 100/20 BID for the remainder of the treatment period. Re-escalation to 125/30 BID or re-titration in cases in which the subject has been off KarXT for a longer period of time (at least a week) is allowed and will require a discussion between the PI and the medical monitor. Additional changes to KarXT dosing (e.g., temporary dose reductions) may be permitted as clinically indicated upon approval by the medical monitor.

Beginning after Visit 5/Day 28, remote interim visits will be completed with flexibility between the in-clinic visits, approximately once every 4 weeks. For interim visits, either a Home Health

Care nurse or the study site staff will visit the subject to complete the scheduled visit. To augment at-home visits, telemedicine should be used at the investigator's discretion to review any information collected during the in-home interim visit. Also, when needed the sites will have the option to schedule a subject for an in-clinic visit in lieu of a remote interim visit.

All subjects will have questionnaires administered throughout the study (see Schedule of Assessments Table 2). Analyses of change from baseline in diagnostic measures will be performed.

Safety will be assessed through spontaneous AEs including AESIs, procholinergic and anticholinergic symptoms; SAEs and AEs leading to discontinuation of KarXT; SAS; BARS; AIMS; body weight; BMI; waist circumference; orthostatic vital signs; clinical laboratory assessments (hematology, clinical chemistry, coagulation, urinalysis, and drug screen), 12-lead ECG; physical examination; and C-SSRS will be evaluated throughout the study as scheduled. Section 11 provides complete details on these safety assessments.

Efficacy will be assessed through PANSS total score, PANSS-positive score, PANSS-negative score, PANSS Negative Marder Factor score, and CGI-S score at scheduled visits. Refer to Section 12 for more details.

Details on PK assessments are provided in Section 13 and include monitoring of trough concentrations at scheduled visits.

Exploratory assessments include cognition testing using CANTAB; prolactin levels; digital biomarkers of schizophrenia (US Only); Ecological Momentary Assessment (EMA) Patient Reported Outcomes (PRO; US Only) and EMA Verbal Learning and Memory Test (VLMT; US Only) which will be evaluated during scheduled visits or on specified study days. See Section 14 for more details.

A safety follow-up/end of study/ET visit (Visit 30/Day 371) will be performed for all subjects after the last dose of KarXT.

An Independent Safety Monitoring Committee (ISMC) will be responsible for periodically reviewing the safety data from this study and confirming that the study may continue.

Table 1 presents the Study Drug Dosing Scheme.

Table 1. Study Drug Dosing Scheme

Period:	Open-Label Extension Treatment[a]							End of Treatment	EOS/ET/UNS
Day:	Day 1	Day 3 +1 day	Day 8[b] ±1 day	Day 14 ±2 days	Day 28[c] ±3 days	Day 56 ±3 days	Days 84 to 350 ±3 days	Day 364 ±3 days	Day 371 ±3 days
Visit:	Visit 1	Visit 2	Visit 3 [b]	Visit 4	Visit 5[c]	Visit 7	Visits 9 to 28	Visit 29	Visit 30
Xanomeline/ trospium (KarXT)*:	50/20 BID	100/20 BID	125/30 BID (Option: 100/20 BID)[d]	125/30 BID (Option: 100/20 BID)[d,e]	125/30 BID (Option: 100/20 BID)[d,e]	125/30 BID (Option: 100/20 BID)[d,e]	125/30 BID (Option: 100/20 BID)[d,e]	125/30 BID (Option: 100/20 BID) [d,e]	N/A
Comment(s):	2-day lead-in dose	Upward titration of dose	Upward titration of dose						7 (±3) days after the last dose or for ET from the study or UNS

Abbreviations: BID = twice daily; EOS = end of study; ET = early termination; N/A = not applicable; PI = principal investigator; UNS = unscheduled.
* All the KarXT doses are in mg xanomeline/mg trospium.

a. At Visit 1 (Day 1) subjects will initiate dosing with KarXT BID independently, at home. Visits 2, 3, 4, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, and 30 are in-clinic/on-site visits. Visits 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28 are interim visits.
b. Subject to receive at least 8 doses of KarXT 100/20 prior to escalating to the KarXT 125/30 dose.
c. Beginning after Visit 5/Day 28, interim visits will be completed with flexibility between in-clinic visits, approximately once every 4 weeks.
d. All subjects who are increased to KarXT 125/30, depending on tolerability, will have the option to return to KarXT 100/20 BID.
e. Re-escalation to 125/30 BID or re-titration in cases where subject has been off KarXT for a longer period of time (at least a week) is allowed and will require a discussion between the PI and the medical monitor. Additional changes to KarXT dosing (e.g., temporary dose reductions) may be permitted as clinically indicated upon approval by the medical monitor.

7.2 Discussion of Study Design

The KarXT clinical development program includes this open-label extension study to evaluate the long-term safety, tolerability, and efficacy data for KarXT in subjects with schizophrenia who participated in either of the 2 Phase 3 double-blind clinical studies and completed the treatment period without any tolerability/safety issues.

This study will allow subjects that were randomized into a preceding Phase 3 study (KAR-007 or KAR-009) to reinstitute (or initiate treatment if a placebo subject) KarXT therapy. Subjects will receive KarXT (with the same lead-in dose of KarXT 50/20 BID), regardless of treatment assignment from the preceding Phase 3 study. Thus, subjects who received placebo during the preceding Phase 3 study who may not have demonstrated clinical benefit, nonetheless, may be considered appropriate for the current study, as all subjects will receive KarXT.

The dosing plan for this study has been established and follows the earlier studies. All eligible subjects will receive the same lead-in doses of KarXT (KarXT 50/20 BID). Dosing will be titrated to 100/20 BID on Day 3 and further titrated to 125/30 BID on Visit 3 (Day 8), unless the subject continues to experience AE(s) from the previous dose increase of KarXT.

During the study, all subjects who are increased to the highest dose of KarXT, depending on tolerability, will have the option to return to the next lower dose of KarXT (100/20 BID). Re-escalation to 125/30 BID or re-titration in cases where subject has been off KarXT for a longer period of time (at least a week) is allowed and will require a discussion between the PI and the medical monitor.

Beginning after Visit 5/Day 28 (approximately 1 month of KarXT treatment), remote interim visits will be completed every 4 weeks between the in-clinic visits, to allow for subject safety monitoring and IP dispensing and accountability. For interim visits, either a Home Health Care nurse or the study site staff will visit the subject to complete the scheduled visit. To augment at-home visits, telemedicine should be used at the investigator's discretion to review any information collected during the in-home interim visit. Also, when needed, the sites will have the option to schedule a subject for an in-clinic visit in lieu of a remote interim visit.

A 52-week treatment phase is considered to be sufficient to demonstrate the long-term safety and tolerability of KarXT. A sample size of approximately 350 subjects is also determined to be an appropriate number of evaluable subjects to assess the long-term safety of KarXT administration. Section 5.2 details the nonclinical and clinical background information available on KarXT, including dose rationale.

7.3 End of Study

A subject will have fulfilled the requirements for study completion if/when the subject has completed the study treatment, including the EOS visit or the last scheduled visit as indicated in the Schedule of Assessments (Table 2) in accordance with the protocol.

7.4 Independent Safety Monitoring Committee

For the purpose of this study, the ISMC is an independent group of individuals with pertinent expertise that reviews on a regular basis accumulating safety and tolerability data from the clinical study. The ISMC will include 3 clinicians and a reporting statistician. This committee will be responsible, on a periodic basis, for confirming the safety and tolerability of KarXT throughout the study, with particular focus on assessing for any new or long-term toxicities that might be involved with KarXT.

The reviews will allow a comparison of event rates and detection of safety signals, and to identify important safety information. The ISMC charter will contain the details of the types of data to be reviewed, the defined triggers for review, the minimum frequency of meetings (timed, if no triggers), and the communication plan for disseminating review recommendations.

8 SELECTION OF STUDY POPULATION

Section 7.1 provides information regarding the number of subjects planned to be enrolled.

8.1 Inclusion Criteria

Individuals must meet all of the following criteria to be included in the study:

1. Subject is aged 18 to 65 years, at time of enrollment into the preceding acute study (KAR-007/009).
2. Subject is capable of providing informed consent.
    a. A signed informed consent form must be provided before any study assessments are performed.
    b. Subject must be fluent in (oral and written) English (United States only) or local language (Ukraine only) to consent.
3. Subject has completed the treatment period on study drug (through Day 35 -2 days) of Studies KAR-007 or KAR-009.
4. Subject resides in a stable living situation, in the opinion of the investigator.
5. Subject has an identified, reliable informant/caregiver willing to be able to address some questions related to certain study visits, if needed. An informant/caregiver may not be necessary if the subject has been the patient of the investigator for ≥1 year.
6. Women of childbearing potential (WOCBP) or men whose sexual partners are WOCBP must be sexually abstinent (in line with their preferred and usual lifestyle) or willing and able to use at least 1 highly effective method of contraception during the study and for at least 7 days after the last dose of KarXT. Sperm donation is not allowed for 7 days after the final dose of KarXT. A female subject is considered to be a WOCBP after menarche and until she is in a postmenopausal state for 12 consecutive months or is otherwise permanently sterile (for which acceptable methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy) [22]. For the definition and list of highly effective methods of contraception, see Appendix 1.

8.2 Exclusion Criteria

Subjects will be excluded from the study if 1 or more of the following criteria is/are applicable:

1. Risk for suicidal behavior during the study as determined by the investigator's clinical assessment and C-SSRS as confirmed by the following:
    a. Subject answers "Yes" to "suicidal ideation" Item 4 (active suicidal ideation with some intent to act, without specific plan) or Item 5 (active suicidal ideation with specific plan and intent) on the C-SSRS assessment.
    b. Nonsuicidal self-injurious behavior is not exclusionary.
2. Any clinically significant abnormality including any finding(s) from the physical examination, vital signs, ECG, or laboratory test at the end-of-treatment visit of Studies

KAR-007 or KAR-009 that the investigator, in consultation with the medical monitor, would consider to jeopardize the safety of the subject.

3. Female subject is pregnant.
4. If, in the opinion of the investigator (and/or Sponsor), subject is unsuitable for enrollment in the study or subject has any finding that, in the view of the investigator (and/or Sponsor), may compromise the safety of the subject or affect his/her ability to adhere to the protocol visit schedule or fulfill visit requirements.
5. Subjects with extreme concerns relating to global pandemics such as coronavirus disease 2019 (COVID-19) that preclude study participation.
6. Risk of violent or destructive behavior.
7. Subjects participating in another investigational drug or device trial or planning on participating in another clinical trial during the course of the study.

8.3 Safety Laboratory Evaluations for Eligibility

Subjects may be enrolled into KAR-008 prior to receipt of the results from the safety laboratory evaluations collected on Visit 10 of the preceding acute study. These subjects will be dosed on Day 1 of KAR-008; however, subjects may be withdrawn from KAR-008 depending upon the clinical significance of the results of the Visit 10 safety laboratory evaluations at the discretion of the PI in consultation with the medical monitor. Abnormal lab values deemed clinically significant must be recorded as AEs. Subjects with elevated liver function tests (LFTs) per the DILI criteria must be withdrawn from further participation in KAR-008. Retesting of labs is allowed x 1 with the exception of elevated LFTs.

8.4 Study Withdrawal, Removal, and Replacement of Subjects

If a subject discontinues study treatment and is withdrawn from the study for any reason, the study site must immediately notify the medical monitor. The date and the reason for study discontinuation must be recorded on the electronic case report form (eCRF). Subjects who complete or discontinue early from the study will be asked to return to the study site within 7 (±3) days of the last administration of KarXT to complete EOS assessments as indicated in the Schedule of Assessments (Table 2).

In the event that a subject discontinues prematurely from the study because of a treatment-emergent AE (TEAE) or serious TEAE, the TEAE or serious TEAE will be followed up until it resolves (returns to normal or baseline values) or stabilizes, or until it is judged by the investigator to no longer be clinically significant.

Once a subject is withdrawn from the study, the subject may not re-enter the study.

A subject may voluntarily withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following:

- progressive disease
- unacceptable toxicity or AE
- subject withdrawal of consent: at any time, a subject's participation in the study may be terminated at his/her request or on the basis of the investigator's clinical judgment; the reason for subject withdrawal will be noted on the eCRF
- intercurrent illness: a condition, injury, or disease unrelated to the primary diagnosis that became apparent during treatment and necessitated the subject's termination from the study
- general or specific changes in the subject's condition that renders them ineligible for further treatment according to the inclusion/exclusion criteria (eg, subject has need for a medication prohibited by the protocol)
- subject fails to adhere to the protocol requirements (eg, drug noncompliance [if a subject is off KarXT for >7 consecutive days])
- violation of entry criteria, ie, enrolled subjects who are later discovered not to meet eligibility criteria
- development of suicidal or assaultive behavior
- alcohol abuse or illegal drug use
- pregnancy, as indicated in Section 11.8
- Sponsor's decision to discontinue study

Subjects who withdraw from the study will be encouraged to complete the same final evaluations as subjects completing the study according to this protocol, particularly safety evaluations. The aim is to record data in the same way as for subjects who completed the study.

Reasonable efforts will be made to contact subjects who are lost to follow-up. A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study center. These efforts must be documented in the subject's file. Subjects with AEs ongoing at end of study will be followed until the AE is resolved or the subject is considered to be in stable condition.

The Sponsor has the right to terminate the study at any time in case of SAEs or if special circumstances concerning the KarXT become known, making further treatment of subjects impossible. In this event, the investigator(s) will be informed of the reason for study termination.

8.4.1 Pregnancy

No evidence of mutagenicity, or treatment effects on reproduction, fertility, or fetal parameters have been demonstrated in animals following administration of xanomeline, but there are no adequate and well-controlled studies in pregnant women (FDA Pregnancy Category B). Animal reproduction studies of trospium chloride have shown an adverse effect on the fetus, but potential benefits may warrant the use of the drug in pregnant women despite the risk (FDA Pregnancy Category C).

Therefore, WOCBP in this study must be willing to use a highly effective method of birth control (see Appendix 1 for a list of acceptable highly effective methods of contraception) during the study and for 7 days after the last dose of KarXT. WOCBP will have a urine pregnancy test on Day 0 (before receiving KarXT) and thereafter, as designated at other scheduled visits (Table 2). In case of positive urine pregnancy test result, a serum sample should be sent to the central laboratory to confirm the result. Pregnant women are excluded from this study because the effects of KarXT on the developing human fetus are unknown with the potential for teratogenic or abortifacient effects.

Because there is an unknown but potential risk for AEs in nursing infants secondary to treatment of the mother with KarXT, women who become pregnant must discontinue KarXT immediately.

The effects of KarXT on sperm are unknown. Male subjects whose sexual partners are WOCBP must agree to use a highly effective method of birth control (see Appendix 1 for a list of acceptable highly effective methods of contraception) and must not impregnate a sexual partner during or for 7 days after the last dose of KarXT. They must also agree to refrain from sperm donation for 7 days after the last dose of KarXT.

WOCBP will be instructed that known or suspected pregnancy occurring during the study should be confirmed and reported to the investigator. If a female subject becomes pregnant, the investigator must withdraw her from the study without delay. The subject must not receive any further doses of the KarXT. The investigator must notify the Sponsor or their designee of any female subject or female partner of a male subject that becomes pregnant while participating in the study. If the female subject or the female partner of the male subject is willing and able to consent to pregnancy follow-up, she will be followed until her pregnancy reaches term. Only those procedures that would not expose the pregnant female patient to undue risk will be performed. See Section 11.8 for further reporting and monitoring details.

Full details of the pregnancy will be recorded on the withdrawal page (exit form) of the eCRF, or a Pregnancy Reporting Form will be completed if the subject has completed the study. Notification of the pregnancy should be submitted via the Pregnancy Reporting Form within 24 hours of knowledge of the pregnancy. Pregnancy is not to be considered an AE; however, it must be reported using the same procedure as described for reporting SAEs, Section 11.7.4.

8.5 Completion of the Study or Lost to Follow-up

The study will be completed when all subjects have completed their study-related procedures in accordance with the protocol.

Every reasonable effort will be made to contact subjects who are lost to follow-up to obtain EOS information. Details regarding follow-up efforts are to be documented in the subject's medical records/source documentation.

8.6 Study Termination

The availability of any new adverse safety information related to KarXT may result in stopping the study. An investigator, Sponsor, or Institutional Ethics Committee (IEC)/Institutional Review Board (IRB) may take such actions. If the study is terminated for safety reasons, subjects will be notified immediately and assured that appropriate treatment and follow-up will be available. If an investigator terminates the study, the Sponsor, subjects, and IEC/IRB will be informed about the reason for such action. Similarly, if the Sponsor terminates the study, it will inform the investigators, the IEC/IRB, and the subjects of the reason for such an action. Similar notifications will be sent by the IEC/IRB if it takes such an action.

9 TREATMENTS

9.1 Details of Study Treatments

KarXT is formulated as hard hydroxypropyl methylcellulose oral capsules containing 2 distinct populations of drug beads, 1 of which is loaded with xanomeline tartrate and the other of which is loaded with trospium chloride. Each capsule contains the free base equivalent of xanomeline and trospium according to the desired dosage strength. In addition to the active ingredients, the drug beads contain microcrystalline cellulose (MCC). The beads are not coated and are formulated for immediate release of the active ingredients.

9.1.1 Identity of Study Treatments

Active study agents for treatment group will be size 0, Swedish orange, opaque, and hydroxypropyl methylcellulose hard capsules. For the 2-day lead-in period (Days 1 and 2), subjects will receive capsule strength KarXT 50/20 BID, followed by 2 capsules of KarXT 50/10 mg BID or a dosage of 100/20 mg BID for a total daily dose of 200/40 mg for the remainder of Week 1 (Days 3 to 7). At the beginning of Visit 3 (Day 8), dosing may be increased to 2 capsules of KarXT 62.5/15 mg or a dosage of 125/30 mg BID for a total daily dose of 250/60 mg, depending on tolerability. Investigators have the option to return a subject to KarXT 100/20 mg BID. Re-escalation to 125/30 BID or re-titration in cases where subject has been off KarXT for a longer period of time (at least a week) is allowed and will require a discussion between the PI and the medical monitor.

Additional changes to KarXT dosing (e.g., temporary dose reductions) may be permitted as clinically indicated upon approval by the medical monitor (see also Section 9.4).

Note: In case of dose reduction, re-escalation, or re-titration, additional PK samples will be collected at 8 and 14 days (+/- 2) post dose change in accordance with the Visits 3 and 4 schedules, unless these additional samples overlap with regularly scheduled PK samples. Otherwise unscheduled visits should be performed to collect these additional samples.

KarXT 50/10 mg is composed of 44.4% xanomeline tartrate, 5.8% trospium chloride, excipients 37.59% MCC, 11.5% lactose monohydrate, 0.3% ascorbic acid and 0.5% talc in a size 0, Swedish orange, hydroxypropyl methylcellulose hard capsule.

KarXT 50/20 mg is composed of 33.4% xanomeline tartrate, 8.7% trospium chloride, excipients 39.8% MCC, 17.3% lactose monohydrate, 0.3% ascorbic acid and 0.5% talc in a size 0, Swedish orange, hydroxypropyl methylcellulose hard capsule.

KarXT 62.5/15 mg is composed of 41.7% xanomeline tartrate, 6.5% trospium chloride, excipients 38.1% MCC, 12.9% lactose monohydrate, 0.3% ascorbic acid and 0.5% talc in a size 0, Swedish orange, hydroxypropyl methylcellulose hard capsule.

All investigational agents are to be stored according to requirements.

9.1.2 Packaging and Labeling

The study packaging and labeling will be performed by Corealis Pharma, located in Laval, Quebec, Canada and Catalent Pharma Solutions, located in Winchester, Kentucky (labelling for the US sites), and Catalent Pharma Solutions, located in Philadelphia, Pennsylvania (labelling for Ukrainian sites). All packaging and labeling operations will be performed according to Good Manufacturing Practice for Medicinal Products and the relevant regulatory requirements.

Bulk supply bottles are labeled with the name of the drug, recommended storage conditions, the name and address of the manufacturer and the Investigational Use Statement (for the US sites: "Caution: New Drug – Limited by Federal [USA] Law to Investigational Use" and for the Ukrainian sites: "For clinical trial use only" or similar wording).

Further details on labeling of investigational product will be provided in the Pharmacy Manual.

Subjects will be provided an automated medication dispenser which will be prefilled with medication at scheduled intervals. Full details on study medication dispensing can be found in the Pharmacy Manual.

9.1.3 KarXT Storage

Prior to dispensing KarXT to the subjects, it must be stored at controlled room temperature 15˚C-25˚C.

9.1.4 KarXT Retention

KarXT must be retained until completion or termination of the study, and written authorization from the Sponsor has been received. All unused and used KarXT must be destroyed at the site or returned, as specified by Sponsor. It is the investigator's responsibility to ensure that the Sponsor has provided written authorization prior to return or destruction, and that appropriate records of the disposal are documented and maintained. No used or unused KarXT may be disposed until fully accounted for by the study monitor.

9.2 Dosage Schedule

Subjects who roll over into KAR-008 will start dosing with KarXT on Day 1 of the current study. Day 0 (baseline) procedures must be completed prior to Day 1 and should be completed the same day as Visit 10 (Day 35) of the preceding acute study KAR-007 or KAR-009. The assessments performed on Visit 10 (Day 35) of Studies KAR-007 or KAR-009 will be considered as baseline assessments along with any additional procedures that will be performed on Day 0 of the current study. Any scheduled Day 0 assessments that were not completed on Day 35 of the acute study (KAR-007 or KAR-009) must be completed on Day 0 of the current study.

The first dose of the KarXT will be self-administered in the morning of Day 1 and the last dose will be self-administered in the morning of EOT Visit (Day 364). KarXT should be administered daily BID on an empty stomach (ie, at least 1 hour before a meal or 2 to 3 hours after a meal).

Some considerations for dosing and PK blood withdrawals are provided in the subsections below. As described in Section 10.2, KarXT dosing adherence will be monitored using AiCure Technology. Additionally, KarXT will be dispensed to individual subjects via MedReady, an automated medication dispenser.

9.2.1 Day 0

- The site pharmacist will prefill the pill trays of two automated medication dispensers with sufficient quantities of KarXT for the first 8 days of dosing (Visits 1-3), one for the morning doses and the other for the evening doses.
- After AiCure training and registration and MedReady activation and training, sites will send the subject home with instruction to begin self-administration of KarXT BID in the morning of Day 1.
- For all KarXT doses, the first dose is to be self-administered in the morning and the evening dose will be self-administered at 12 (±4.5) hours after the morning dose.

9.2.2 Visit 1/Day 1 Dosing

- Initiate BID dosing with KarXT 50/20 x 4 doses.
- All subjects must have taken 4 doses of the KarXT 50/20 before dose escalation to KarXT 100/20 BID. As the medication dispenser will be prefilled with the prescribed next dose of KarXT, subjects should be instructed to contact the investigator in the event they did not take all 4 doses of KarXT 50/20 prior to Visit 2/Day 3.

9.2.3 Visit 2/Day 3 Dosing

- Initiate BID dosing with KarXT 100/20 x 10 doses.
- All the subjects must have taken at least 8 doses of the KarXT 100/20 before dose escalation to KarXT 125/30 BID. As the medication dispenser will be prefilled with the prescribed next dose of KarXT, subjects should be instructed to contact the investigator in the event they did not take at least 8 doses of KarXT 100/20 prior to Visit 3/Day 8.
- Remind subject to hold the morning dose on day of next clinic visit (Visit 3/Day 8) as that dose will be taken while at the clinic, after the pre-dose PK sample is drawn.
- Remind the subject to bring allocated MedReady dispensers to the next clinic visit.

9.2.4 Visit 3/Day 8

- If dose escalation to the KarXT 125/30 level is confirmed by investigator order on Visit 3/Day 8, initiate BID dosing of KarXT 125/30
- The first morning dose of KarXT 125/30 at Visit 3 is to be administered in the clinic (after the pre-dose PK blood draw) (Table 2).
- If the use of visit windows becomes necessary, PK sampling **must** accompany the actual day of uptitration for Visit 3/Day 8.

- 3 PK samples will be collected at pre-dose in the morning, 1 hour (±10 min), and 2 hours (±10 min) post-dose.
- The site pharmacist will prefill two MedReady pill dispensing trays with sufficient quantities of KarXT to continue BID dosing until next clinic visit/assessment for tolerability.(until Visit 4), one for the morning doses and the other for the evening doses.
- The pharmacist or site staff may swap out the used pill trays in the allocated Medready dispensers with the new refilled supply.
- Remind subject to hold the morning dose on day of next clinic visit (Visit 4/Day 14) as that dose will be taken while at the clinic, after the pre-dose PK sample is drawn.
- Remind the subject to bring allocated MedReady dispensers to the next clinic visit.

In the event that the subject is not escalated to KarXT 125/30 at Visit 3, in accordance with investigator order, dispense sufficient quantities of KarXT 100/20 to continue BID dosing until next clinic visit/assessment for tolerability.

9.2.5 Visit 4/Day 14 Dosing and PK Considerations

- If dose of KarXT 125/30 BID was confirmed by investigator order on Visit 3/Day 8, the site pharmacist will prefill 2 MedReady pills trays with sufficient quantities of KarXT 125/30 to continue BID dosing until next clinic visit/assessment for tolerability.(until Visit 5), one tray for the morning doses and the other for evening doses.
- The pharmacist or site staff may swap out the used pill trays in the allocated Medready dispensers with the new refilled supply.
- The first morning dose of KarXT at Visit 4 is to be administered in the clinic (after the pre-dose PK blood draw) (Table 2).
- If the use of visit windows becomes necessary, PK sampling **must** accompany the actual day of uptitration for Visit 4/Day 14.
- 3 PK samples will be collected at pre-dose in the morning, 1 hour (±10 min), and 2 hours (±10 min) post-dose.
- Remind the subject to bring allocated MedReady dispensers to the next clinic visit.

In the event that the subject was not escalated to KarXT 125/30 at Visit 3, in accordance with investigator order, dispense sufficient quantities of KarXT 100/20 to continue BID dosing until next clinic visit/assessment for tolerability.

9.2.6 Visits 5-29 Dosing and PK Considerations

- For each study visit, the site pharmacist will prefill two MedReady pill dispensing trays with sufficient quantities of KarXT for the next 14 days of dosing (Visits 5-29), one for the morning doses and the other for the evening doses, in accordance with the investigator order, confirming prescribed KarXT dose.

- The pharmacist, site staff, or home health care staff may swap out the used pill trays in the allocated Medready dispensers with the new refilled supply, depending upon the visit location (in-clinic versus remote).
- Remind the subject to bring allocated MedReady dispensers to each in-clinic visit for refill.
- For Days 84, 168, and 364, collection of a single PK sample before the morning dose is preferred. However, timing of the sample is not mandatory and will not be captured as a protocol deviation if collected after the morning dose (but must be collected on required visit day).
- See Section 9.4.1 for management of KarXT dose changes and PK sampling.

9.3 Measures to Minimize Bias: Study Treatment Assignment

9.3.1 Method of Study Treatment Assignment

The 9-digit Subject Number previously assigned to the subject in the Study KAR-007/KAR-009 will continue to be used in the current Study KAR-008. This number will be associated with the subject throughout the current study.

9.3.2 Blinding

This is an open-label study; therefore, blinding is not applicable.

9.4 Dosage Modification

Subjects will self-administer the KarXT as described in Section 7.1 and in accordance with the Schedule of Assessments (Table 2). The KarXT doses were selected based on the previous preclinical and clinical studies (see Section 5.2). Per the protocol, subjects will be evaluated for dose adjustments starting at Visit 3 through the remainder of the treatment period (see Section 9.2).

Additional changes to KarXT dosing (e.g., temporary dose reductions) may be permitted as clinically indicated upon approval by the medical monitor.

9.4.1 Dose Modifications and PK Sampling Considerations

In case of dose reduction, re-escalation, or re-titration, additional PK samples should be collected at 8 and 14 days (+/- 2) post dose change in accordance with the Visits 3 and 4 schedules, unless these additional samples overlap with regularly scheduled PK samples. Otherwise unscheduled visits should be performed to collect these additional samples.

9.4.2 Extended Dosing Interruptions and Re-titration

Re-escalation to 125/30 BID or re-titration in cases where subject has been off the KarXT for a longer period of time (at least a week) is allowed and will require a discussion between the principal investigator (PI) and the medical monitor.

All subjects approved by the PI and medical monitor will resume KarXT by repeating the lead-in dosing scheme used at the start of study. Subjects will start with a lead-in dose of KarXT 50/20 BID for the first 2 days after restarting study drug. Then the dose will be titrated to 100/20 BID for at least the next 4 days, allowing the subject to adjust to KarXT before receiving a higher dose of 125/30 BID after restarting study drug, unless the subject is continuing to experience AEs from the previous dose, in which case the subject will remain on KarXT 100/20 BID.

9.5 Treatment Accountability and Compliance

The pharmacist or other designated individual will maintain records of study treatment delivered to the study site, the inventory at the study site, the distribution to each subject, and the return of materials to the Sponsor or designee for storage or disposal. These records should include dates, quantities, batch/serial numbers, expiration dates, temperature log, and unique code numbers assigned to the product and study subjects.

Administration of KarXT will be supervised by study site personnel (during in-clinic visits) and by a digital compliance tool to ensure adherence (AiCure technology). Also, KarXT will be dispensed using MedReady time-controlled dispensing device, which dispenses KarXT at scheduled intervals. Subjects will be advised to return the MedReady device to the site staff at each in-clinic visit for drug accountability and refilling.

At all dispensing visits, the empty or unused MedReady pill trays will be collected by the Home Health Care nurse and/or site staff, depending upon visit location (ie, in-clinic or remotely in home). In case a Home Health Care nurse performs the interim visit, they will perform a preliminary drug accountability before shipping the empty or partially empty pill trays to the study site for final accountability check. Full details can be found in the Pharmacy Manual.

Investigators will maintain records that adequately document that the subjects were provided with the correct study treatment supply and reconcile the usage of the study drug. Investigational product will not be returned to the Sponsor or designee or destroyed until accountability has been fully monitored through the end of the study. KarXT accountability will be assessed periodically by the assigned study monitor.

9.6 Prior and Concomitant Therapy

9.6.1 Prior and Concomitant Medications

Concomitant medications ongoing as of Visit 10/Day 35 of the preceding acute study (KAR-007 or KAR-009) will be captured in the eCRF as baseline therapy. Thereafter, all medications and other treatments taken by the subject during the study, including those treatments initiated before the start of the study drug administration, must be recorded on the KAR-008 eCRF.

Restricted prior therapies are provided below.

During the study (ie, from the time of enrollment at baseline visit [Day 0] until study completion [EOT/ET]), subjects should refrain from the use of any new concomitant medications without the prior approval of the investigator. The administration of any other concomitant medications during the study period is prohibited without the prior approval of the investigator unless its use is deemed necessary in a medical emergency. Any medication or therapy that is taken by or administered to the subject during the course of the study must be recorded in the eCRF. The entry must include the dose, regimen, route, indication, and dates of use.

All the subjects enrolled into the study must not take the below mentioned prohibited medications for the duration of the treatment period.

- Oral antipsychotic medications, monoamine oxidase inhibitors, mood stabilizers (ie, lithium), anticonvulsants (eg, lamotrigine, Depakote), tricyclic antidepressants (eg, imipramine, desipramine), selective serotonin reuptake inhibitors, or any other psychoactive medications except for anxiolytics that were taken on an as needed basis (eg, lorazepam, chloral hydrate).
- Long acting injectable antipsychotics (including INVEGA TRINZA®).

Note: Please direct questions relating to prohibited medications to the medical monitor.

9.6.2 Concomitant Medications for Anxiety and/or Sleep Aid

Subjects are allowed to take benzodiazepines (up to 4 mg lorazepam/day or equivalent) for anxiety, agitation, and insomnia on a PRN basis. Subjects may also use non-benzodiazepine medications (eg, zolpidem, zaleplon) as a sleep aid, also on a PRN basis. Study sites must record the use of such medications in the eCRF and subject's source document.

Note: Cognition testing should not be done within 8 hours of receiving a benzodiazepine or sleep medication.

10 STUDY PROCEDURES

Table 2 outlines the timing of procedures and assessments to be performed throughout the study. Section 11.6 specifies laboratory assessment samples to be obtained. See Sections 11, 12, 13, and 14 for additional details regarding efficacy, safety, PK, and exploratory assessments, respectively.

See Appendix 3 for alternative visit procedures that may be used to replace scheduled on-site study visits during COVID-19 pandemic-related quarantine or mandated physical distancing.

COVID-19 testing will be completed in accordance with clinical site standard operating procedures. If a subject tests positive for COVID-19 during the study, they may be quarantined as needed and any scheduled visits should be rescheduled or alternative procedures (see Appendix 3) may be followed at the discretion of the investigator. If the subject requires hospitalization, an SAE should be reported and the subject should be followed up as outlined in Section 11.7.3.

Table 2. Schedule of Assessments

DAY	0	1	3 (+1d)	8 (± 1d)	14 (± 2d)	28 (± 3d)	42 (± 3d)	56 (± 3d)	70 (± 3d)	84 (± 3d)	98 (± 3d)	112 (± 3d)	126 (± 3d)	140 (± 3d)	154 (± 3d)	168 (± 3d)
WEEK		**1**			**2**	**4[a]**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**
VISIT	**Baseline[1]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
TYPE OF VISIT	Clinic		Clinic	Clinic	Clinic	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic
PROCEDURE																
Written informed consent	X															
Subject eligibility verification	X															
Urine pregnancy test (WOCBP only)[b]	(X)[2]			X		X		X		X		X		X		X
Urine drugs of abuse and alcohol testing[c]	(X)[2]		X	X	X	X		X		X		X		X		X
Review of inclusion/exclusion criteria	X															
Height, body weight, BMI, waist circumference[d]	X				X			X		X		X		X		X
Complete physical examination[e]	X															
Targeted physical examination[f]	(X)[2]			X	X	X		X		X		X		X		X
Spontaneous AEs[g]	X		X	X	X	X		X		X		X		X		X
Review of concomitant medications[h]	X		X	X	X	X		X		X		X		X		X
Vital signs: BP and HR[i]	X		X	X	X	X		X		X		X		X		X
Resting ECG (12-lead)[j]	X				X							X				
Blood samples for clinical laboratory tests[k]	X				X	X			X			X			X	
Blood sample for prolactin	X				X							X				
Functional constipation inquiry[l]	X		X	X	X	X		X		X		X		X		X
Interim clinical observations[m]							X		X		X		X		X	
Safety follow up of any AE and/or conmed changes reported by the HHC staff, as needed[n]							X		X		X		X		X	
Determination of dose titration				X	X											
PK blood draw[o]				X	X					X						X

DAY	0	1	3 (+1d)	8 (± 1d)	14 (± 2d)	28 (± 3d)	42 (± 3d)	56 (± 3d)	70 (± 3d)	84 (± 3d)	98 (± 3d)	112 (± 3d)	126 (± 3d)	140 (± 3d)	154 (± 3d)	168 (± 3d)
WEEK		**1**			**2**	**4[a]**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**
VISIT	**Baseline[1]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
TYPE OF VISIT	Clinic		Clinic	Clinic	Clinic	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic
PROCEDURE																
PANSS[p]	X				X	X		X		X		X		X		X
C-SSRS[q]	X			X	X	X		X		X		X		X		X
CGI-S scale	X				X	X		X		X		X		X		X
Cognition testing[r]	X					X		X		X						X
SAS	X					X						X				
BARS	X					X						X				
AIMS	X					X						X				
AiCure registration and training[s]	X															
MedReady registration and training[s]	X															
KarXT dispensed using MedReady[s]	X			X	X	X	X	X	X	X	X	X	X	X	X	X
Subject self-administration of KarXT using AiCure app		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EMA registration and training[t]			X													
EMA PRO[u]			X		X	X		X		X		X		X		X
EMA VLMT[v]						X		X		X		X		X		X
Digital biomarkers using AiCure app[w]			X	X	X	X		X		X		X		X		X

Table 2 Schedule of Assessments (Continued from Visits 16 to 30)

DAY	182 (± 3d)	196 (± 3d)	210 (± 3d)	224 (± 3d)	238 (± 3d)	252 (± 3d)	266 (± 3d)	280 (± 3d)	294 (± 3d)	308 (± 3d)	322 (± 3d)	336 (± 3d)	350 (± 3d)	364 (± 3d)	371 (± 3d)
WEEK	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52**	**53**
VISIT	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29 (EOT)**	**30 (EOS/ET/UNS)[3]**
TYPE OF VISIT	Interim	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic	Clinic
PROCEDURE															
Urine pregnancy test (WOCBP only)[b]		X		X		X		X		X		X		X	X
Urine drugs of abuse and alcohol testing[c]		X		X		X		X		X		X		X	X
Height, body weight, BMI, waist circumference[d]		X		X		X		X		X		X		X	X
Complete physical examination[e]															X
Targeted physical examination[f]		X		X		X		X		X		X		X	
Spontaneous AEs[g]		X		X		X		X		X		X		X	X
Review of concomitant medications[h]		X		X		X		X		X		X		X	X
Vital signs: BP and HR[i]		X		X		X		X		X		X		X	X
Resting ECG (12-lead)[j]		X						X						X	
Blood samples for clinical laboratory tests[k]		X			X			X			X			X	
Blood sample for prolactin		X						X						X	
Functional constipation inquiry[l]		X		X		X		X		X		X		X	X
Interim clinical observations[m]	X		X		X		X		X		X		X		
Safety follow up of any AE and/or conmed changes reported by the HHC staff, as needed[n]	X		X		X		X		X		X		X		
PK blood draw[o]														X	X
PANSS[p]		X		X		X		X		X		X		X	X

DAY	182 (± 3d)	196 (± 3d)	210 (± 3d)	224 (± 3d)	238 (± 3d)	252 (± 3d)	266 (± 3d)	280 (± 3d)	294 (± 3d)	308 (± 3d)	322 (± 3d)	336 (± 3d)	350 (± 3d)	364 (± 3d)	371 (± 3d)
WEEK	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52**	**53**
VISIT	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29 (EOT)**	**30 (EOS/ET/UNS)[3]**
TYPE OF VISIT	Interim	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic	Clinic
PROCEDURE															
C-SSRS[q]		X		X		X		X		X		X		X	X
CGI-S scale		X		X		X		X		X		X		X	X
Cognition testing[r]						X						X			X
SAS		X						X						X	X
BARS		X						X						X	X
AIMS		X						X						X	X
KarXT dispensed using MedReady dispenser[s]	X	X	X	X	X	X	X	X	X	X	X	X	X		
Subject self-administration of KarXT using AiCure app[s]		X	X	X	X	X	X	X	X	X	X	X	X	X	
EMA PRO[u]		X		X		X		X		X		X			
EMA VLMT[v]		X		X		X		X		X		X			
Digital biomarkers using AiCure app[w]		X		X		X		X		X		X			

Abbreviations: AE = adverse event; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; BL = baseline; BMI = body mass index; BP = blood pressure; CGI-S = Clinical Global Impression–Severity scale; C-SSRS = Columbia-Suicide Severity Rating Scale; d = day; ECG = electrocardiogram; EMAW = EMA Wellness; EOS = end of study; EOT = end of treatment; ET = early termination; HR = heart rate; PANSS = Positive and Negative Syndrome Scale; PK = pharmacokinetic; QTcF = QT interval corrected by Fridericia; SAS = Simpson-Angus Rating Scale; UNS = unscheduled visit.

See Appendix 3 for alterative visit procedures that may be used to replace scheduled on-site study visits during COVID-19 pandemic-related quarantine or mandated physical distancing.

1. Baseline Day 0 assessments should be rolled over from Day 35/Visit 10 of the preceding study (KAR-007/009) whenever possible (exception: cognition which should be rolled over from Day 32). Includes pregnancy testing, complete physical exam, vital signs, ECG, safety laboratory evaluations, functional constipation inquiry, PANSS, C-SSRS, CGI-S, SAS, AIMS and BARS.
2. (X) = optional. See accompanying footnote for details
3. Other assessments as needed.

a. Beginning after Visit 5/Day 28, interim visits will be completed every 2 weeks with flexibility between the in-clinic visits, which will occur every month. For interim visits, either a Home Health Care nurse or the study site staff will visit the subject to complete the scheduled visit. Telemedicine should be utilized at the investigator's discretion to complete a portion of a visit or follow-up on information collected. Also, when needed, the sites will have the option to schedule a subject for an in-clinic visit in lieu of an interim visit.
b. A urine pregnancy test for WOCBP should be performed at scheduled visits. If a urine pregnancy test is positive, a serum sample should be sent to central laboratory for confirmation of the result. A new urine pregnancy test should be performed on Day 0 visit only if subject left the inpatient unit after completion of Visit 10 of the preceding acute study but prior to completion of the Day 0 procedures of the current study.
c. A National Institute on Drug Abuse-5 (NIDA-5) urine drug screen (cannabinoids or marijuana, phencyclidine, amphetamines, opiates, and cocaine) and test for alcohol (breathalyzer or blood alcohol level) will be performed at the indicated scheduled visits. Should be performed on Day 0 visit only if subject left the inpatient unit after completion of Visit 10 of the preceding acute study but prior to completion of the Day 0 procedures of the current study.
d. Baseline height is recorded from Study KAR-007/KAR-009 Screen visit. Baseline body weight, BMI and waist circumference recorded from KAR-007/009 Visit 10. At the indicated study visits, body weight and waist circumference will be measured and BMI calculated.
e. A complete physical examination includes body temperature (°C), general appearance, head/eyes/ears/nose/throat (HEENT), examination of thorax and, assessment of cardiac, musculoskeletal, and circulatory systems, palpations for lymphadenopathy, and limited neurological examination.
f. A targeted physical examination includes at a minimum body temperature, a check of general appearance, as well as examination of organ systems that are relevant to the investigator based on review of the subject's reported AEs, review of systems, or concomitant medication use. These also include symptom-driven physical examinations which will be performed as clinically indicated at any study visit. A targeted physical examination at Day 0 is optional, and only required if the subject has reported a new AE in the time since completing Visit 10 of the preceding acute study.
g. Adverse events as reported by subjects or observed by clinical staff. Adverse events ongoing as of Visit 10 of the preceding acute study will be recorded in the KAR-008 Medical History eCRF. Adverse events occurring after dosing with KarXT in the current study will be recorded in the KAR-008 AE eCRF. One PK blood sample may be drawn if a relevant/significant AE (based on medical judgment) is reported during a scheduled visit or if there is a dose titration or a relevant/significant AE reported during an unscheduled visit (no multiple draws).
h. Concomitant medications ongoing as of Visit 10/Day 35 of the preceding acute study will be captured in the eCRF as baseline therapy. Thereafter, all medications and other treatments taken by the subject during the study, including those treatments initiated before the start of the study, must be recorded on the KAR-008 eCRF.
i. Vital signs measurements should be taken at all in-clinic visits, while the subject is supine and standing after 2 minutes. BP includes systolic and diastolic BP and is to be taken in the same arm for the duration of the study. During in-clinic visits orthostatic vital signs should occur 2 (±1) hours after morning dose of KarXT whenever possible.
j. ECG should be obtained within 1 to 2 hours post morning dose whenever possible. ECG at all indicated visits should be performed before blood withdrawal for any safety laboratory tests and/or PK analysis. ECGs will be transmitted electronically to a central reader for determination of ventricular rate (bpm), PR (msec), QRS (msec), QT (msec), and QTcF (msec) measurements.
k. Refer to Section 11.6 for individual laboratory tests. For urinalysis, a urine dipstick will be performed at the site. In the event of abnormalities, the sample will be sent to the central laboratory for full microscopic urinalysis. At the indicated interim visits the safety laboratory evaluations samples will be collected by the home care health nurse or site staff.
l. Functional constipation inquiry: At specified visits, subjects will be asked whether they have experienced constipation (per the ROME III criteria and Bristol Stool Form Scale; see Appendix 2) since the last visit and if yes, whether the constipation required intervention. If the subject answers yes, sites are instructed to ask subjects to provide event date and ensure the event is documented as an AE and treatment is documented as concomitant medication.

m. Interim clinical observations include collection of vital signs, review of spontaneous AEs, and concomitant medications. These assessments will be performed by a Home Health Care (HHC) nurse and/or site staff visiting the patient at home. Vital signs measurements should be taken at all interim visits, while the subject is supine and standing after 2 minutes. BP includes systolic and diastolic BP and should be taken in the same arm for the duration of the study whenever possible.
n. For any new AEs or concomitant medication reported by the HHC nurse, site staff must follow up with subjects directly via telemedicine over telephone or through video chat and complete a safety follow-up evaluation.
o. PK blood samples will be collected in the morning before dosing on Days 8, 14, 84, 168 and 364. On Days 8 and 14, three PK samples will be collected at pre-dose in the morning, 1 hour (±10 min), and 2 hours (±10 min) post-dose. For Days 84, 168, and 364, collection of a single sample before the morning dose is preferred. However, timing of the sample is not mandatory and will not be captured as a protocol deviation if collected after the morning dose (but must be collected on required visit day). Note: In cases of dose reduction, re-escalation, or re-titration, additional PK samples should be collected at 8 and 14 days (+/- 2) post dose change in accordance with the Visits 3 and 4 schedules, unless these additional samples overlap with regularly scheduled PK samples. Otherwise unscheduled visits should be performed to collect these additional samples.
p. It is recommended, if at all possible, that the PANSS assessment should be performed before all the other scale assessments for all visits at which it is performed.
q. The "since last visit" version should be used for C-SSRS administration. At the Unscheduled visit, the C-SSRS should be performed to monitor subjects for suicidality.
r. Cognition testing is performed using CANTAB. Cognition testing should not be done within 8 hours of receiving a benzodiazepine or sleep medication. Cognition testing at Visit 30 will only be performed if the visit is a result of Early Termination of a subject.
s. Refer to the Study Operations Manual for details.
t. Refer to the Study Operations Manual for details.
u. EMA PRO will be completed by the subject at home on a cellular device 3 times per day for 7 days every 28 days, beginning on Day 29. An abbreviated version of the assessment will be utilized on Days 4-6 and 15-17 to familiarize subjects with the process. Refer to Study Operational Manual for details.
v. Cognitive insight will be assessed using the EMA VLMT. The assessment will be completed by the subject at home on a cellular device 1 time per day for 3 days every 28 days beginning on Day 32. Refer to Study Operational Manual for details.
w. Digital biomarkers of schizophrenia will be calculated through completion of a smartphone-based assessment daily by the subject for 3 days collected initially on Days 4-6, 9-11, and 15-17. Subsequently subjects will complete assessments daily for 3 days every 28 days, beginning on Day 29. Refer to Study Operational Manual for details.

10.1 Informed Consent

Informed consent forms must be approved for use by the reviewing Independent Ethics Committee (IEC)/Institutional Review Board (IRB). Before performing any study-related procedures, the investigator (or designee) will obtain written informed consent from the subject and/or caregiver (Ukraine only).

10.2 Study Procedures

Assessments and their timing are to be performed as outlined in the Schedule of Assessments (Table 2). Section 11.6 specifies laboratory assessment samples to be obtained.

Safety assessments are described in Section 11 and include spontaneous AEs including AESIs; procholinergic and anticholinergic symptoms, SAEs and AEs leading to discontinuation of the KarXT; SAS; BARS; AIMS; body weight; BMI; waist circumference; orthostatic vital signs; ECG; clinical laboratory assessments (hematology, clinical chemistry, coagulation, urinalysis, and drug screen); physical examination; and C-SSRS.

Efficacy assessments are described in Section 12 and include PANSS and CGI-S scores.

PK assessments are described in Section 13 and include monitoring of trough concentrations of xanomeline and trospium.

Exploratory assessments are described in Section 14 and include cognition testing using CANTAB; prolactin levels; digital biomarkers of schizophrenia; EMA PRO; and EMA VLMT.

The investigator may, at his/her discretion, arrange for a subject to have an unscheduled assessment, especially in the case of AEs that require follow-up or are considered by the investigator to be possibly related to the use of KarXT. The unscheduled visit page in the eCRF must be completed. The assessments and procedures that may be performed during an unscheduled visit are outlined in the Schedule of Assessments (Table 2). Additional assessments can be performed as needed, at the discretion of the investigator, and following discussion with the medical monitor.

Study discontinuation procedures are described in Section 8.4 and Section 8.6.

10.2.1 AiCure Adherence Technology

The AiCure technology will be used to monitor study medication adherence in all subjects, both in the US and the Ukraine. Additionally, the AiCure technology will be used to capture Digital Biomarker Assessment of schizophrenia symptoms of subjects in the US only.

Medication Adherence (US and Ukraine):

This study will employ a medication adherence monitoring platform (herein after referred to as Platform) for all subjects in the study. The Platform uses artificial intelligence on smartphones to confirm medication ingestion. In addition, built-in reminders and a communication system allow real-time intervention in case of drug interruptions.

Use of this Platform will in no way supersede or replace the physician and/or prescribed medication protocol of the subjects. Because the Platform does not change the medication protocol of the subjects, but rather encourages adherence to the predefined protocol, use of this Platform presents minimal risk to the subjects. Use of the Platform will be required for all subjects in the study.

The monitoring Platform requires that all subjects take each dose of the medication while using a smartphone. Participants will download the AiCure application on their personal smartphone device; for participants who do not have a smartphone or do not wish to use their personal smartphone, site personnel will provide the participant with one of the preloaded backup provisioned devices.

When at home, study subjects will receive a medication reminder at a time within a predefined window. This notification reminds subjects to take their medication dose while using the Platform. Subjects will follow a series of prescribed steps in front of the front-facing webcam to visually confirm their ingestion of the medication. The application on the smartphone will make an automated determination of whether the subject has properly taken their medication at the prescribed time. There is no need for a healthcare provider to review the administration, nor would a healthcare provider need to be available at the time the subject takes their medication. The amount of guidance that the device provides to the subject is automatically reduced as the subject becomes more proficient at using the application.

Digital Biomarker Assessment (US only):

For subjects enrolled at US sites only, subjects will be performing brief smartphone-based assessments using the AiCure application. Video and audio of participant behavior captured during these assessments will be used to calculate visual and auditory markers of schizophrenia symptomatology. These digital biomarkers will be used as exploratory efficacy endpoints to measure change from baseline in disease severity. See Section 14.4 for endpoint discussion. The material will be presented to subjects in one of two ways. In the first, material will be presented to subjects, and will include questionnaires provided at regular intervals during the study. Images may also be shown to subjects, and they will be asked to describe each image in a few sentences to the camera of the smartphone.

Data Collected on the AiCure Platform:

After the device confirms proper medication ingestion, video recordings will be encrypted and transmitted to a secure centralized location for further analysis, including testing for duplicate enrollment. Video and audio recordings from the Digital Biomarker assessments will be encrypted and transmitted in a similar manner. The captured data and video is reviewable through a roles and rules restricted system ensuring privacy of the information. The system is compliant with applicable US and European data privacy laws, including General Data Protection Regulation (GDPR) (EU) 2016/679 the Health Insurance Portability and Accountability Act (HIPAA), which protects the privacy and security of healthcare information.

Phone numbers of the patients may also be collected and stored in an encrypted manner. Storing the phone numbers will allow for direct communication with patients, including automated messaging from the Platform device and contact by healthcare providers or other monitoring personnel. At no time is the phone number visible to healthcare providers or monitoring personnel. Individuals outside the clinical sites will not be provided with patient names, nor will they be given access to patient medical records.

The Platform may provide significant benefits to study subjects as well as to the other stakeholders in the trial. Subjects will benefit from rapid and tailored intervention in case of non-adherence (drug interruptions) without having to visit the clinic for unscheduled visits. Healthcare providers will have access to real-time and continuous adherence data without having to rely on self-reported data or frequent study visits by patients. Subjects who regularly fail to take their medication will be contacted by healthcare providers or other study monitoring personnel for retraining.

11 SAFETY ASSESSMENTS

Safety assessments (spontaneous AEs including AESIs; procholinergic and anticholinergic symptoms; SAEs and AEs leading to discontinuation of the KarXT; SAS; BARS; AIMS; body weight; BMI; waist circumference; orthostatic vital signs; ECG; clinical laboratory assessments [hematology, clinical chemistry, coagulation, urinalysis, and drug screen]; physical examination; and C-SSRS) will be performed at protocol-specified visits, as specified in the Schedule of Assessments (Table 2).

11.1 Demographics, Medical History, and Psychiatric History

Demographic data, and medical and psychiatric history will be recorded from the Phase 3, double-blind, acute study (KAR-007/KAR-009).

Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs on the eCRF in accordance with Section 11.7. All changes that are not present at baseline or described in the past medical history and identified as clinically noteworthy must be recorded as AEs.

11.2 Vital Signs

Orthostatic vital signs (systolic and diastolic BP and heart rate measurements) will be evaluated at all scheduled visits indicated in the Schedule of Assessments (Table 2). All vital signs will be measured supine and standing after 2 minutes. Blood pressure measurements are to be taken in the same arm for the duration of the study. During in-clinic visits, beginning with Visit 2 (Day 3), orthostatic vital signs should occur 2 (±1) hours after morning dosing, whenever possible.

Vital sign measurements will be repeated if clinically significant or machine/equipment errors occur. Out-of-range BP, or heart rate measurements will be repeated at the investigator's discretion. Any confirmed, clinically significant vital sign measurements must be recorded as AEs.

11.3 Complete/Targeted Physical Examination

A complete physical examination (body temperature, general appearance, head/eyes/ears/nose/throat [HEENT], examination of thorax and abdomen, assessment of cardiac, musculoskeletal, and circulatory systems, palpations for lymphadenopathy, and limited neurological examination) will be performed at visits as specified in Table 2. Physical examinations will be performed by a physician.

A targeted physical examination includes at a minimum body temperature, a check of general appearance, as well as examination of organ systems that are relevant to the investigator, based on review of the subject's reported AEs, review of systems, or concomitant medication use. These also include symptom-driven physical examinations which will be performed as clinically indicated at any study visit.

11.4 Weight, Height, Body Mass Index, and Waist Circumference

The baseline height measurement will be recorded from the lead-in Study KAR-007/009 Screen visit. The baseline body weight, BMI and waist circumference measurements will be recorded from the KAR-007/009 Visit 10. At the indicated visits of the current study (Table 2), body weight and waist circumference will be measured and BMI calculated. All findings should be recorded in the eCRF.

11.5 Electrocardiograms

A 12-lead, resting ECG should be obtained within 1 to 2 hours post morning dose at the visits indicated in the Schedule of Assessments (Table 2). ECG at all scheduled visits should be performed before blood withdrawal for any safety laboratory tests and/or PK analysis.

ECGs will be transmitted electronically to a central reader for determination of ventricular rate (bpm), PR (msec), QRS (msec), QT (msec), and QTcF (msec) measurements. An assessment of normal or abnormal will be recorded; if the ECG is considered abnormal, the abnormality will be documented on the eCRF. ECGs will be repeated if clinically significant abnormalities are observed or artifacts are present.

11.6 Laboratory Assessments

Laboratory assessment samples (Table 3) are to be obtained at designated visits as detailed in the Schedule of Assessments (Table 2).

Table 3. Laboratory Assessments

Hematology	**Serum Chemistry**	**Urine Analysis (Dipstick)**
Full and differential blood count Hct Hb MCH MCHC MCV Platelet count RBC count WBC count with differential	Albumin ALT ALP AST Albumin Uric acid BUN or urea Carbon dioxide Creatinine Creatine kinase and subtypes Electrolytes (sodium, potassium, chloride, calcium, phosphorus) GGT Glucose LDH Total bilirubin Direct bilirubin Total cholesterol HDL LDL Triglycerides Total protein	Appearance pH Protein Glucose Ketone bodies Indicators of blood and WBCs Specific gravity Urobilinogen Occult blood WBCs
HbA1c	**Prolactin**	
Coagulation		
PT Activated PTT Fibrinogen		
Pregnancy test: A urine pregnancy test for WOCBP should be performed per the schedule of assessments (Table 2). In case of positive urine pregnancy test result, a serum sample should be sent to the central laboratory to confirm the result.		
Full and microscopic urinalysis: Chemical exam: SG, pH, bilirubin, urobilinogen, protein, glucose, ketone, hemoglobin, myoglobin, leukocyte esterase, nitrite, ascorbic acid Microscopic exam: RBCs, WBCs, epithelial cells, bacteria, yeasts, parasites, casts, crystals		

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; GGT = gamma-glutamyl transpeptidase; HCG = human chorionic gonadotropin; Hb = hemoglobin; Hct = hematocrit; HDL = high density lipoprotein; LDH = lactate dehydrogenase; LDL = low density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; WBC = white blood cell; WOCBP = women of childbearing potential.

Venous blood of approximately 12 to 20 mL will be withdrawn for the tests listed above at scheduled time points as per Table 2.

A minimum volume of 10 mL will be obtained to perform urinalysis (if abnormalities observed on dipstick) and urine drug screen at scheduled time points as per Table 2.

Blood and urine samples (microscopic analysis) will be analyzed at a central laboratory facility. Urine samples will first be analyzed by dipstick at the site. If the results of the dipstick indicate abnormalities to be further investigated, the sample will be sent to the central laboratory and a microscopic analysis will be performed. All laboratory reports must be reviewed, signed, and dated by the investigator. A legible copy of all reports must be filed with both the subject's eCRF and medical record (source document) for that visit. Any laboratory test result considered by the investigator to be clinically significant should be considered an AE (clinically significant AEs include those that require an intervention). Clinically significant abnormal values occurring during the study will be followed up until repeat test results return to normal, stabilize, or are no longer clinically significant.

All the study subjects will be closely monitored for the drug-induced liver toxicity (detailed in Section 11.7.5), during the study.

Other Laboratory Assessments:

- A National Institute on Drug Abuse-5 (NIDA-5) urine drug screen (cannabinoids or marijuana, phencyclidine, amphetamines, opiates, and cocaine) will be performed using a dipstick throughout the study.
- Alcohol testing will be performed using a breathalyzer or blood alcohol test.

11.7 Adverse Events

11.7.1 Adverse Events

An AE is any symptom, physical sign, syndrome, or disease that either emerges during the study or, if present at screening/baseline, worsens during the study, regardless of the suspected cause of the event. All medical and psychiatric conditions (except those related to the indication under study) present at screening/baseline will be documented in the medical history eCRF. Changes in these conditions and new symptoms, physical signs, syndromes, or diseases should be noted on the AE eCRF during the rest of the study. Clinically significant laboratory abnormalities should also be recorded as AEs. Surgical procedures that were planned before the subject enrolled in the study are not considered AEs if the conditions were known before study inclusion; the medical condition should be reported in the subject's medical history.

In accordance with the protocol, the investigator and/or study staff will elicit AEs and intercurrent illness during and at the end of the study period and these will be recorded on the appropriate page of the eCRF. Adverse events will be elicited by asking the subject a nonleading question, for example, "Have you experienced any new or changed symptoms since we last

asked?" The eCRF will be completed at the end of the study as soon as the results of the final lab tests are available.

Each AE is to be documented on the eCRF with reference to date of onset, duration, frequency, severity, relationship to KarXT, action taken with KarXT, treatment of event, and outcome. Furthermore, each AE is to be classified as being serious or nonserious. Changes in AEs and resolution dates are to be documented on the eCRF.

For the purposes of this study, the period of observation for collection of AEs extends from the time immediately after the administration of KarXT on Day 1 until the EOS or ET. Follow-up of the AE, even after the date of therapy discontinuation, is required if the AE persists until the event resolves or stabilizes at a level acceptable to the investigator.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the event should be noted. If the intensity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

The severity of AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 5.0 (Grades 1 through 5).

Specific guidelines for classifying AEs by intensity and relationship to KarXT are given in Table 4 and Table 5.

Table 4. Classification of Adverse Events by Intensity

MILD: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
MODERATE: An event that is sufficiently discomforting to interfere with normal everyday activities.
SEVERE: An event that prevents normal everyday activities.

Table 5. Classification of Adverse Events by Relationship to KarXT

UNRELATED: This category applies to those AEs that are clearly and incontrovertibly due to extraneous causes (disease, environment, etc).
UNLIKELY: This category applies to those AEs that are judged to be unrelated to the test drug but for which no extraneous cause may be found. An AE may be considered unlikely to be related to KarXT if or when it meets 2 of the following criteria: (1) it does not follow a reasonable temporal sequence from administration of the test drug; (2) it could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it does not follow a known pattern of response to the test drug; or (4) it does not reappear or worsen when the drug is readministered.
POSSIBLY: This category applies to those AEs for which a connection with the test drug administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related if or when it meets 2 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; or (3) it follows a known pattern of response to the test drug.
PROBABLY: This category applies to those AEs that the investigator feels with a high degree of certainty are related to the test drug. An AE may be considered probably related if or when it meets 3 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not be

reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose (note that there are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists; for example, as in bone marrow depression, fixed drug eruptions, or tardive dyskinesia); or (4) it follows a known pattern of response to the test drug.
DEFINITELY: This category applies to those AEs that the investigator feels are incontrovertibly related to test drug. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose and recurs with re-exposure to drug (if rechallenge occurs); and (4) it follows a known pattern of response to the test drug.

Abbreviation: AE = adverse event.

11.7.2 Adverse Events of Special Interest

The AEs of special interest will be monitored and include orthostasis and liver function test elevations inclusive of drug-induced liver injury (DILI).

11.7.3 Serious Adverse Events

An SAE is any untoward medical occurrence, in the view of either the investigator or Sponsor, that:

- results in death,
- is life-threatening,
- results in inpatient hospitalization or prolongation of existing hospitalization (however, hospitalization for elective treatment of a pre-existing non-worsening condition is not considered an SAE; the details of such hospitalizations must be recorded on the medical history or physical examination page of the eCRF),
- results in persistent or significant disability/incapacity, and/or
- is a congenital anomaly/birth defect.

Other important medical events that may not be immediately life-threatening or result in death or hospitalization, based upon appropriate medical judgment, are considered SAEs if they are thought to jeopardize the subject and/or require medical or surgical intervention to prevent 1 of the outcomes defining an SAE. Serious AEs are critically important for the identification of significant safety problems; therefore, it is important to take into account both the investigator's and the Sponsor's assessment. If either the Sponsor or the investigator believes that an event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting.

11.7.4 Serious Adverse Event Reporting

An SAE occurring from the time the first dose of KarXT is administered, during the study, or within 1 week of stopping the treatment must be reported to the Catalyst Clinical Research Pharmacovigilance group and will be communicated to the Sponsor. Any such SAE due to any cause, whether or not related to the KarXT, must be reported within **24 hours of occurrence or when the investigator becomes aware of the event**. Notification can be made using email.

Catalyst Clinical Research Pharmacovigilance email address: [redacted]

The event must be recorded on the standard AE eCRF. Preliminary reports of SAEs must be followed up by detailed descriptions later on, including clear and anonymized photocopies of hospital case reports, consultant reports, autopsy reports, and other documents when requested and applicable. SAE reports must be made whether or not the investigator considers the event to be related to the investigational drug.

Appropriate remedial measures should be taken to treat the SAE, and the response should be recorded. Clinical, laboratory, and diagnostic measures should be employed as needed in order to determine the etiology of the problem. The investigator must report all additional follow-up evaluations to the Catalyst Clinical Research Pharmacovigilance group within 24 hours of becoming aware of the additional information or as soon as is practicable. All SAEs will be followed up until the investigator and Sponsor agree the event is satisfactorily resolved.

Any SAE that is not resolved by the end of the study or upon discontinuation of the subject's participation in the study is to be followed up until it either resolves, stabilizes, returns to baseline values (if a baseline value is available), or is shown to not be attributable to the KarXT or procedures.

11.7.5 Drug-Induced Liver Injury

The sponsor has incorporated the following for monitoring of drug-induced liver injuries:

- *An increase of serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) to >3 × ULN should be followed by repeat testing within 48 to 72 hours of all 4 of the usual serum measures (ALT, AST, ALP, and total bilirubin) to confirm the abnormalities and to determine if they are increasing or decreasing. An inquiry should be made about the symptoms (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, and rash).*
- *Close observation should be initiated with ALT or AST >3 × ULN:*
    - *Repeat liver enzyme and serum bilirubin tests 2 or 3 times weekly. The frequency of retesting can decrease to once per week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic.*
    - *Obtain a more detailed history of symptoms and prior or concurrent diseases.*

- *Obtain a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.*
- *Rule out acute viral hepatitis types A, B, C, D, and E, autoimmune or alcoholic hepatitis, non-alcoholic steatohepatitis, hypoxic/ischemic hepatopathy, and biliary tract disease.*
- *Obtain a history of exposure to environmental chemical agents.*
- *Obtain additional tests to evaluate liver function, as appropriate (eg, international normalized ratio, and/or direct bilirubin).*
- *Consider gastroenterology or hepatology consultations.*

- *Discontinuation of treatment should be considered if:*
  - *ALT or AST >8 × ULN*
  - *ALT or AST >5 × ULN for more than 2 weeks*
  - *ALT or AST >3 × ULN and (total bilirubin >2 × ULN or international normalized ratio >1.5)*
  - *ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (>5%)*
- *Hepatic adjudication of cases should include an evaluation for alternative causes such as viral, autoimmune, alcohol, hepatobiliary disorders, non-alcoholic steatohepatitis, concomitant medications, etc.*
- *Follow-up to resolution of elevated liver enzymes.*
- *Gamma-glutamyl transferase elevations alone should not prompt drug discontinuation.*

Subjects must be monitored closely. If close monitoring is not possible, the study drug should be discontinued.

11.7.5.1 Trial Discontinuation Criteria Other than DILI and Pregnancy

11.7.5.2 Individual Stopping Criteria

Based on NCI CTCAE v5.0, study drug will be discontinued in any subject who has a ≥ Grade 4 AE. Discontinuation or reduction in the dosage of the study drug for Grade 3 AEs other than DILI AEs (see Section 11.7.5) will be at the discretion of the investigator.

11.7.5.3 Trial Stopping Rules

The safety and tolerability aspects of KarXT will be overseen by an ISMC. The ISMC will meet periodically and review the unblinded data and will be responsible for advising the sponsor on ways to safeguard the interests of the clinical study subjects. The committee is expected to recommend sponsor whether to:

a. Continue the clinical study without modification; or
b. Continue the clinical study with modification (listing the specific modifications recommended); or
c. Terminate the study.

11.7.6 Suspected Unexpected Serious Adverse Reactions

Adverse events that meet all of the following criteria will be classified as suspected unexpected serious adverse reactions (SUSARs) and reported to the appropriate regulatory authorities in accordance with applicable regulatory requirements for expedited reporting:

- serious
- unexpected (ie, the event is not consistent with the safety information in the IB or package insert of generic trospium)
- there is at least a reasonable possibility that there is a causal relationship between the event and the study treatment

The investigator will assess whether an event is causally related to study treatment. The Sponsor (or Syneos Health) will consider the investigator's assessment and determine whether the event meets the criteria for being reportable as a 7-day or 15-day safety report. SUSARs that are fatal or life-threatening must be reported to the regulatory authorities and the IEC/IRBs (where required) within 7 days after the Sponsor (or Syneos Health) has first knowledge of them, with a follow-up report submitted within a further 8 calendar days. Other SUSARs must be reported to the relevant regulatory authorities and the IEC/IRBs within 15 calendar days after the Sponsor (or Syneos Health) first has knowledge of them.

The Sponsor (or Syneos Health) is responsible for reporting SUSARs and any other events required to be reported in an expedited manner to the regulatory authorities and for informing investigators of reportable events, in compliance with applicable regulatory requirements within specific timeframes. Investigators will notify the relevant IEC/IRBs of reportable events within the applicable timeframes.

11.7.7 Warnings and Precautions

Risk of Urinary Retention:

Trospium chloride tablets should be administered with caution to subjects with clinically significant bladder outflow obstruction because of the risk of urinary retention.

Angioedema:

Angioedema of the face, lips, tongue, and/or larynx has been reported with trospium chloride, the active ingredient in trospium chloride tablets. In one case, angioedema occurred after the first dose of trospium chloride. Angioedema associated with upper airway swelling may be life-threatening. If involvement of the tongue, hypopharynx, or larynx occurs, trospium chloride should be promptly discontinued and appropriate therapy and/or measures necessary to ensure a patent airway should be promptly provided.

Decreased Gastrointestinal Motility:

Trospium should be administered with caution to subjects with GI obstructive disorders because of the risk of gastric retention. Trospium chloride, like other antimuscarinic agents, may decrease GI motility and should be used with caution in subjects with conditions such as ulcerative colitis, intestinal atony, and myasthenia gravis.

Controlled Narrow-angle Glaucoma:

In subjects being treated for narrow-angle glaucoma, trospium chloride should only be used if the potential benefits outweigh the risks and in that circumstance only, with careful monitoring.

Central Nervous System Effects:

Trospium chloride is associated with anticholinergic CNS effects. A variety of CNS anticholinergic effects have been reported, including dizziness, confusion, hallucinations, and somnolence. Subjects should be monitored for signs of anticholinergic CNS effects, particularly after beginning treatment or increasing the dose. Advise subjects not to drive or operate heavy machinery until they know how trospium chloride affects them. If a subject experiences anticholinergic CNS effects, dose reduction or drug discontinuation should be considered.

Anticholinergic Adverse Reactions in Subjects with Moderate Renal Impairment:

Trospium is substantially excreted by the kidney. The effects of moderate renal impairment on systemic exposure are not known but systemic exposure is likely increased. Therefore, anticholinergic adverse reactions (including dry mouth, constipation, dyspepsia, urinary tract infection, and urinary retention) are expected to be greater in subjects with moderate renal impairment.

Elevation of liver enzymes:

Elevated liver enzymes have been reported in previous studies of xanomeline alone in Alzheimer's disease patients. It is notable however, the hepatic enzyme elevations were not observed in the Phase 1 studies in healthy volunteers and that the liver function test elevations observed in the Phase 2 schizophrenia study (KAR-004) with KarXT (a combination of xanomeline and trospium) were quite limited in contrast to the effects observed with xanomeline in the elderly Alzheimer's population. Moreover, even in the Alzheimer disease patients who experienced more hepatic enzyme elevations, the data demonstrate reversibility even with continued xanomeline treatment in those patients where there was sufficient follow-up data. Importantly, there were no Hy's law cases or elevations in total bilirubin to a value of >2X upper limit of reference range in either the xanomeline or KarXT datasets.

11.8 Pregnancy

WOCBP must have a negative pregnancy test at baseline (Day 0).

The investigator must notify the Sponsor (or designee) of any female subject or female partner of a male subject that becomes pregnant while participating in the study. Any known cases of pregnancy will be reported until the subject completes or withdraws from the study.

The pregnancy will be reported immediately by faxing/emailing a completed pregnancy report to the Sponsor (or designee) within 24 hours of knowledge of the event. The pregnancy will not be processed as an SAE; however, the investigator will follow-up with the subject until completion of the pregnancy and must assess the outcome in the shortest possible time, but not more than 30 days after completion of the pregnancy.

If a female subject becomes pregnant, the investigator must withdraw her from the study without delay. The subject must not receive any further doses of the KarXT. Upon discontinuation from the study, only those procedures that would not expose the subject to undue risk will be performed.

If the female subject or the female partner of the male subject is willing and able to consent to pregnancy follow-up, she will be followed until her pregnancy reaches term. Information regarding the pregnancy must only be submitted after obtaining written consent from the pregnant partner. The investigator will arrange counseling for the pregnant partner by a specialist to discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

The investigator should notify the Sponsor (or designee) of the pregnancy outcome by submitting a follow-up pregnancy report. If the outcome of the pregnancy involved spontaneous or therapeutic abortion (any congenital anomaly detected in an aborted fetus is to be documented), stillbirth, neonatal death, or congenital anomaly, the investigator will report the event by faxing/emailing a completed pregnancy report form to the Sponsor (or designee) within 24 hours of knowledge of the event. This event is considered as an SAE.

The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a subject is subsequently found to be pregnant after inclusion in the study, any pregnancy will be followed to term, and the status of mother and child will be reported to the Sponsor after delivery.

11.9 Overdose

The investigator must immediately notify the Sponsor of any occurrence of overdose with KarXT (total daily dose greater than 250/60 mg).

Signs and symptoms of overdose may vary considerably. They are usually manifested by increasing GI stimulation with epigastric distress, abdominal cramps, diarrhea and vomiting, excessive salivation, pallor, cold sweating, urinary urgency, blurring of vision, and eventually fasciculation and paralysis of voluntary muscles. Miosis, increases or decreases in blood pressure with or without bradycardia, and severe anxiety and panic may occur.

Supportive treatment should be used as indicated (artificial respiration, maintenance of airway, oxygen, etc). Atropine sulfate should be available for IV or intramuscular administration. Several

doses ranging from 0.5 to 2.0 mg may be required. Epinephrine 0.1 to 1.0 mg subcutaneous may also be of value in overcoming severe cardiovascular or bronchoconstrictor responses.

Adverse events associated with overdoses should be reported on the eCRF.

11.10 Simpson-Angus Rating Scale

The SAS is an established instrument to measure drug-related extrapyramidal syndromes. It is a 10-item testing instrument used to assess gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, head dropping, glabella tap, tremor, and salivation. The range of scores is from 0 to 40 with increased scores indicating increased severity.

11.11 Barnes Rating Scale for Akathisia

The Barnes Rating Scale for akathisia is a rating scale used to assess the severity of drug-induced akathisia, or restlessness, involuntary movements and inability to sit still. The range of scores is 0 to 14, with higher scores indicating greater severity.[23]

11.12 Abnormal Involuntary Movement Scale

The AIMS is a rating scale that is used to measure involuntary movements know as tardive dyskinesia, which can sometimes develop as a side effect of long-term treatment with antipsychotic medications. It is a 12-item scale to assess orofacial, extremity, and truncal movements as well as the overall severity, incapacitation, and the subject's level of awareness of the movements. Items are scored from 0 (none) to 4 (severe). A higher score indicates more severe dyskinesia.

11.13 Columbia-Suicide Severity Rating Scale

The C-SSRS is a tool designed to systematically assess and track suicidal AEs (suicidal behavior and suicidal ideation) throughout the study.[24] The strength of this suicide classification system is in its ability to comprehensively identify suicidal events while limiting the over-identification of suicidal behavior. The scale takes approximately 5 minutes to administer. The C-SSRS will be administered by a trained rater at the site.

11.14 Functional Constipation Inquiry

Constipation refers to bowel movements that are infrequent or hard to pass.[25] The stool is often hard and dry.[26] Other symptoms may include abdominal pain, bloating, and feeling as if one has not completely passed the bowel movement.[27] The normal frequency of bowel movements in adults is between 3 per day and 3 per week.[25] Constipation will be defined per the Rome III criteria, as less than 3 bowel movements per week, Appendix 2 (Longswreth,1486,C3).[28]

The Bristol Stool Form Scale has been correlated with a change in intestinal function, and has been shown to be a useful tool in clinical practice and research.[29] A sample Bristol Stool Form Scale is located in Appendix 2.

As a measure of anticholinergic effects, at specified visits (Table 2), subjects will be asked whether they have experienced constipation per the ROME III criteria since the last visit, and if yes, whether the constipation required intervention. If the subject answers yes, sites are instructed to ask subjects to provide event date and ensure event is documented as an AE and treatment is documented as concomitant medication. Subjects will not be required to collect and present their stool sample, nor will clinic staff be required to corroborate the subject assessment.

Additional attention can be given to other complaints as well including: straining with bowel movements, excessive time needed to pass a bowel movement, hard stools, pain with bowel movements secondary to straining, abdominal pain, abdominal bloating, and the sensation of incomplete bowel evacuation.[27, 30]

Treatment of constipation depends on the underlying cause and the duration that it has been present. For the purposes of constipation complaints during a clinical trial, the use of laxatives of a bulk forming agent, osmotic agent, stool softener, or lubricant type may be used.

As definitions of constipation are typically based on a history of at least a week, site physician discretion will be allowed for initiation of such treatments.

12 EFFICACY ASSESSMENTS

The Schedule of Assessments (Table 2) outlines the efficacy assessments to be performed throughout the study and their timing.

12.1 Positive and Negative Syndrome Scale

The PANSS is a clinician-administered scale used for measuring symptom severity of subjects with schizophrenia and is widely used in the study of antipsychotic therapy.[31] The PANSS rating form contains 7 positive symptom scales, 7 negative system scales, and 16 general psychopathology symptom scales. Subjects are rated from 1 to 7 on each symptom scale. The positive symptoms in schizophrenia are the excess or distortion of normal function such as hallucinations, delusions, grandiosity, and hostility, and the negative symptoms in schizophrenia are the diminution or loss of normal functions. It takes approximately 45 to 50 minutes to administer. PANSS total score is the sum of all scales with a minimum score of 30 and a maximum score of 210.

It is recommended, if at all possible, that the PANSS assessment should be performed before all the other scale assessments for all visits at which it is performed.

12.2 Clinical Global Impression-Severity

The CGI-S is a rating scale, completed independently by a clinician that is used to measure illness and symptom severity in subjects with mental disorders. It is used to rate the severity of a subject's illness at the time of assessment. The CGI-S modified asks the clinician 1 question: *"Considering your total clinical experience, how mentally ill is the subject at this time?"* The clinician's answer is rated on the following 7-point scale: 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill subjects.[32]

This rating is based upon observed and reported symptoms, behavior, and function in the past 7 days. As symptoms and behavior can fluctuate over a week, the score should reflect the average severity level across the 7 days.

13 PHARMACOKINETICS

13.1 Pharmacokinetic Sampling

13.1.1 PK Blood Samples and Timing

Blood samples for the analysis of xanomeline and trospium levels will be collected at the time points indicated in the Schedule of Assessments (Table 2). Approximately 4 ml of blood will be collected at each scheduled time point. The actual date and time of each blood sample collection will be recorded.

On Days 8 and 14, a total of 3 PK samples will be collected at pre-dose in the morning, 1 hour (±10 min), and 2 hours (±10 min) after the morning dose. For Days 84, 168, and 364, a single sample before the morning dose will be collected. The time windows must be adhered to for the Day 8 and 14 samples. For other visits where PK samples are drawn preferred timing is prior to morning dose of KarXT for the day but is not mandatory. With the exception of Days 8 & 14, PK samples not drawn prior to the day's morning dose of KarXT will not be captured as protocol deviations.

13.1.2 PK Blood Samples and KarXT Dosing Changes

In cases of dose reduction, re-escalation, or re-titration, additional PK samples should be collected at 8 and 14 days (+/- 2) post dose change in accordance with the Visits 3 and 4 schedules, unless these additional samples overlap with regularly scheduled PK samples. Otherwise unscheduled visits should be performed to collect these additional samples.

A single PK sample may be drawn (preferably in the morning) if a relevant/significant AE is reported during a scheduled visit, or if there is a dose adjustment or relevant/significant AE reported during an unscheduled visit (no multiple draws). For ET that is related to an AE, the collection of a PK blood sample is not optional and should be drawn.

Details of PK blood sample collection, processing, storage, and shipping procedures will be provided in a separate laboratory manual.

13.2 Pharmacokinetic Analytical Methodology

The concentration of trospium and xanomeline will be determined from the plasma PK samples using a validated analytical method. Details of the method validation and sample analysis will be included with the final clinical study report.

14 EXPLORATORY ASSESSMENTS

The exploratory assessments cognition testing, prolactin levels, digital biomarkers, EMA PRO, and EMA VLMT will be performed at scheduled visits or study days, as per the Schedule of Assessments (Table 2).

14.1 Cognition Testing - Cambridge Neuropsychological Test Automated Battery

The computerized CANTAB provides an objective measure of cognitive function correlated to neural networks. A short cognitive battery measuring core cognitive domains of impairment in schizophrenia (ie, as per Brief Assessment of Cognition Schizophrenia key cognitive domains) will be employed for this study, and it will take approximately 30 minutes to complete. These CANTAB tests meet MATRICS workshop criteria.[33] Subjects will perform the test on a provisioned iPad with data immediately uploaded to the CANTAB Connect cloud-based platform (Wi-Fi permitting).

Cognition testing should not be done within 8 hours of receiving benzodiazepine or sleep medications.

Table 6. Cognitive Tests and Cognitive Domains Assessed by the Cambridge Neuropsychological Test Automated Battery

CANTAB Tests	MATRICS Cognitive Domain	Outcome Measures
Rapid visual information processing	Sustained attention/vigilance	**A' Prime:** Signal detection measure of how good the subject is at detecting the target sequence (string of three numbers); regardless of response tendency
Verbal recognition memory	Verbal memory and new learning	**Free Recall:** The total number of words that are correctly recalled from the presentation phase by the subject during the immediate free recall stage
Spatial Span	Working memory	**Forward Span Length:** The longest sequence of boxes successfully recalled by the subject
One-touch stockings of Cambridge	Executive Function Planning/Problem Solving	**Problems Solved on First Choice:** The total number of assessed trials where the subject chose the correct answer on their first attempt

Abbreviation: CANTAB = Cambridge Neuropsychological Test Automated Battery

14.2 Change in Prolactin

Blood samples to assess the change in prolactin levels will be obtained on scheduled visits as specified in Table 2.

14.3 Digital Biomarkers of Schizophrenia (US only)

Study subjects will be performing brief smartphone-based assessments using the AiCure application mentioned in Section 10.2.1. Video and audio of participant behavior captured during these assessments will be used to calculate visual and auditory markers of schizophrenia symptomatology. These digital biomarkers will be used as exploratory efficacy endpoints to measure change from baseline in disease severity. The following exploratory endpoints will be collected:

- Overall emotional expressivity
- Positive emotional expressivity
- Negative emotional expressivity
- Audio intensity / speech volume Fundamental frequency of voice
- Formant frequencies of voice
- Vocal jitter
- Vocal shimmer
- Pause lengths during speech
- Lexical diversity
- Rate of speech
- Euclidean head movement
- Rotational head movement

14.4 EMA Wellness Assessments

14.4.1 EMA Wellness – EMA PRO (US only)

EMA is an ambulatory data collection technique that allows the real-time in vivo assessment of functioning behaviors. In the present study, EMA Patient Reported Outcomes (PRO) will be used to assess the subject's functioning associated to negative symptoms and psychotic symptoms in schizophrenia through the use of smartphones for subjects enrolled at US sites only.

EMA PRO surveys are multiple choice questions about the subject's current location, if they are alone or with others, and activities and moods in the last hour. A pop-up visualization will signal participants, 3 times per day for 7 days, to respond to very brief (e.g., 3 minutes) questionnaires about their activities, mood, and symptom experiences during the last hour, per the Schedule of Assessments (Table 2). An abbreviated EMA PRO survey, collecting only information on the subject's location, alone or with others, and activities and moods will be given 3 times per day for 3 days starting on Day 4 and Day 15. Daily assessment times will be adjusted to accommodate each subject's typical sleep and wake schedules.

14.4.2 EMA Wellness - VLMT (US only)

Cognitive insight assessment will be conducted through testing on the Verbal Learning and Memory Test (VLMT), which will be completed by subjects enrolled at US sites only. This assessment will be performed at home on a cellular device 1 time per day for 3 days every 28 days beginning on Day 32. During each VLMT administration, subjects will be presented with a list of 6-, 12-, or 18- words over in 3 separate trials each lasting 30 seconds. Immediately following each exposure to the list, subjects will be shown target and recognition foil words one-by-one and asked to indicate whether or not the word appeared on the list.

In order to examine response bias and the ability to self-evaluate memory performance, immediately after each recognition trial, the subjects will be asked to indicate how many words they believe that they got correct. They will also be asked how well they did as compared to the previous trial and at the end of the 3 trials they will be asked if they improved over the 3 learning trials.

14.4.3 Data Collected on EMAW Platform

Data are encrypted and uploaded to secure servers whenever the phone is connected to Wi-Fi or if cellular data is available. If a Wi-Fi and cellular data are unavailable, EMA response data will be transferred during in-clinic visits.

During each EMA PRO, subjects will be asked about their location (home vs away and where if away); they will also be asked if they are alone or with others, and about their activities, symptoms of schizophrenia, and moods in the last hour.

Data collected during the VLMT include the identification of target words and rejections of foils. The participants will also provide an immediate estimate of their memory task performance as soon as each recognition trial is over.

15 STATISTICAL ANALYSIS

A statistical analysis plan (SAP) will be prepared after the protocol is approved. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. The SAP will serve as a complement to the protocol and supersedes it in case of differences.

The statistical evaluation will be performed using SAS® software version 9.4 or higher (SAS Institute, Cary, NC). All data will be listed, and summary tables will be provided. Summary statistics will be presented by dose group. For continuous variables, data will be summarized with the number of subjects (N), mean, standard deviation, median, minimum, and maximum by treatment group. For categorical variables, data will be tabulated with the number and proportion of subjects for each category by treatment group. No statistical hypothesis testing will be performed.

15.1 Determination of Sample Size

As the primary objective of this study is to assess the long-term safety and tolerability of KarXT, the number of subjects anticipated is based on the number of subjects recruited into and completing the acute studies (KAR-007, KAR-009) and meeting the eligibility requirements for KAR-008.

15.2 Analysis Populations

Enrolled population: All subjects who have given informed consent for KAR-008.

Safety population: All subjects who receive at least 1 dose of KarXT during the current study will be included in the safety population and will be used in the safety analysis.

Modified ITT (mITT) population: All subjects who are enrolled, received at least 1 dose of KarXT, and have a valid PANSS assessment at KAR-008 baseline will be included in the mITT population and will be used in the efficacy analysis.

PK population: All subjects who have received at least 1 dose of KarXT and have at least 1 measurable plasma concentration of KarXT will be included in the PK population.

15.3 Safety Analysis

Safety endpoints will be summarized for all subjects in the Safety population. The presentation of safety data will be based on the treatment received in KAR-008.

All reported AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.1 or higher. The incidence of TEAEs (defined as events with an onset date on or after the first dose of KarXT) will be summarized by System Organ Class and Preferred Term. All AEs will be listed by subject, along with information regarding onset, duration, relationship and severity to KarXT, action taken with KarXT, treatment of event, and outcome.

Orthostatic vital signs, clinical laboratory data, prolactin levels, ECG parameters, and physical examinations will be summarized using descriptive statistics, including observed and change from baseline values, as well as numbers of subjects with values outside limits of the normal range at each time point. Similar descriptive summaries will be provided for C-SSRS, SAS, BARS, AIMS, body weight, BMI, and waist circumference.

15.4 Efficacy Analysis

Efficacy analyses will be summarized based on the mITT population. The summaries described in this section will provide data on maintenance of effect of open-label KarXT over 52 weeks. As these variables are summarized over time and the initial values can be impacted by the treatment received in the acute study, the presentation will use a combination of acute/extension study treatment groups, which is intended to provide perspective on the change in these values from the acute study through the treatment period of KAR-008. Tabular presentations will display descriptive statistics for Baseline of the acute study and the observed and change from baseline study results by scheduled visit for KAR-008.

Responder efficacy variables (PANSS responders) will be summarized descriptively. Response will be derived relative to the acute study Baseline assessment.

Continuous efficacy variables based on the change from baseline (PANSS, CGI-S) will be summarized using descriptive statistics by scheduled visit. Tabular presentations will display descriptive statistics for the Baseline of the acute study and the observed and change from baseline results by scheduled visit for KAR-008. Figures for selected variables will also be generated in order to demonstrate the kinetics of response over time.

15.5 Pharmacokinetic Analysis

Plasma concentrations of xanomeline and trospium will be listed for all subjects. The profiles or time points obtained with protocol deviations affecting PK results will be flagged and may be excluded from summaries and analyses.

The data will be presented graphically via individual plots and mean plots summarized by visit, and time point.

15.6 Exploratory Analysis

The following will be summarized using descriptive statistics: change in cognition using CANTAB; digital biomarkers of schizophrenia; EMA PRO and EMA VLMT.

Further details will be provided in the SAP.

15.7 Interim Analysis

No interim analysis is planned for this study.

15.8 Handling of Missing Data

For responder efficacy variables (PANSS responders), missing data may be handled by non-responder imputation, meaning that subjects who discontinue early or who have missing data at a given time point are imputed as though they did not achieve the given response. Supportive summaries will be based on observed case data.

For continuous efficacy variables based on the change from baseline (PANSS, CGI-S), summaries will be based on observed case data.

Additional methods of missing data imputation may be explored and will be outlined in the SAP.

16 STUDY MANAGEMENT

16.1 Approval and Consent

16.1.1 Regulatory Guidelines

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the US Code of Federal Regulations (CFR), in compliance with International Council for Harmonisation (ICH) and good clinical practice (GCP) guidelines, and all applicable local, state and federal government regulations and laws.

16.1.2 Institutional Review Board/Independent Ethics Committee

Conduct of the study must be approved by an appropriately constituted IEC/IRB. Approval is required for the study protocol, protocol amendments (if applicable), IB, ICFs, recruitment material and subject information sheets and other subject-facing material.

16.1.3 Informed Consent

For each study subject, written informed consent will be obtained before any protocol-related activities. As part of this procedure, the PI or designee must explain orally and in writing the nature of the study, its purpose, procedures, expected duration, alternative therapy available, and the benefits and risks involved in study participation. The subject should be informed that they may withdraw from the study at any time, and the subject will receive all information that is required by local regulations and guidelines for ICH. The PI will provide the Sponsor or its representative with a copy of the IEC-/IRB-approved ICF before the start of the study.

The ICF should be revised whenever there are substantial changes to procedures or when new information becomes available that may affect the willingness of the subject to participate. Revisions to the consent form required during the study must be approved by the Sponsor and IEC/IRB, and a copy of the revised consent form is provided to the Sponsor. For any updated or revised consent forms, the subjects must be re-consented for continued participation in the study.

A pregnant partner consent form should be obtained before collecting any data from a female pregnant partner of a male subject, if she becomes pregnant during the course of the study or within 1 week of the last dose of KarXT.

A caregiver consent must be obtained (Ukraine only) before collecting any data from a caregiver pertaining to him or her and the subject.

<u>Subject Registry</u>

Clinical trial registries, such as clinical trial subject database (CTSdatabase, US only) and Verified Clinical Trials (VCT, US and Ukraine), seek to reduce duplicate enrollment by identifying potential protocol violations and duplicate subjects before randomization. At the time of providing the informed consent for the initial KAR-007 or -009 study, the investigator or

designee will have explained the IRB/IEC-approved Subject Database Authorization to the subject and witnessed the signature. That executed authorization form remains in effect for KAR-007 and KAR-008 or KAR-009 and KAR-008 study participation.

At the beginning of screening for KAR-007 or KAR-009, following consents execution and subject number assignment and before other study procedures, site staff that had received training and login information access (www.subjectregistry.com) to the database entered the subject study ID number and authorized subject identifiers. Two reports, one from CTS and one from VCT, detailing any potential protocol violations or dual enrollment attempts were generated and were printed for source documentation. The reports detailed each protocol violation detected and specific washout period dates where applicable.

At participating sites in the Ukraine, only VCT was used to verify participants' current and past research study status. Following proper regionally compliant informed consent and after obtaining a subject number from IXRS, each Ukraine based KAR-009 participant was checked in the VCT database. Partial identifiers were utilized.

Throughout the initial KAR-007 or KAR-009 study, and during this open label extension study, tracking of actively enrolled subjects will continue based on updates by coordinators in the interactive response system. At the last subject contact, CTSdatabase and VCT staff will automatically close out the subject (safety follow-up, ET, or completer) based on interactive response system (IXRS).

16.2 Data Handling

Any data to be recorded directly on the eCRFs (to be considered as source data) will be identified at the start of the study. Data reported on the eCRF that are derived from source documents should be consistent with the source documents, or the discrepancies must be explained. See also Section 16.3.

Clinical data will be entered by site personnel on eCRFs for transmission to the Sponsor. Data on eCRFs transmitted via the web-based data system must correspond to and be supported by source documentation maintained at the study site unless the study site makes direct data entry to the databases for which no other original or source documentation is maintained. In such cases, the study site should document which eCRFs are subject to direct data entry and should have in place procedures to obtain and retain copies of the information submitted by direct data entry. All study forms and records transmitted to the Sponsor must only include coded identifiers such that directly identifying personal information is not transmitted. The primary method of data transmittal is via the secure, internet-based electronic data capture (EDC) system maintained by Syneos Health. Access to the EDC system is available to only authorized users via the study's secure internet web site, where a user unique assigned username and password are required for access.

Any changes made to data after collection will be made through the use of the EDC system. Electronic CRFs will be considered complete when all missing and/or incorrect data have been resolved.

16.3 Source Documents

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. The investigator will provide direct access to source documents and/or source data in the facilitation of trial-related monitoring, audits, review by IECs/IRBs, and regulatory inspections.

The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, not obscure the original entry, and be explained if necessary.

Data recorded on source documents will be transcribed onto eCRFs. Copies of completed eCRFs will be provided to the Sponsor and the sites at the end of the study. The completed eCRFs will be retained by the investigator.

16.4 Record Retention

Study records and source documents must be preserved for at least 15 years after the completion or discontinuation of/withdrawal from the study, at least 2 years after the drug being studied has received its last approval for sale, or at least 2 years after the drug development has stopped, and in accordance with the applicable local privacy laws, whichever is the longer time period.

The investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of subject health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR, Parts 160 and 164 (the HIPAA of 1996 Privacy Regulation). The investigator shall ensure that study subjects authorize the use and disclosure of protected health information in accordance with HIPAA Privacy Regulation and in a form satisfactory to the Sponsor.

16.5 Monitoring

The study will be monitored according to the KAR-008 monitoring plan to ensure that it is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements.

Monitoring visits may include on-site or remote visits and may also utilize periodic telephone contacts. The PI will assure they and adequate site personnel are available throughout the study to collaborate with clinical monitors. Clinical monitors must have direct access to source documentation in order to check the completeness, clarity, and consistency of the data recorded in the eCRFs for each subject.

The investigator will make available to the clinical monitor all source documents and medical records necessary to review protocol adherence and eCRFs. In addition, the investigator will work closely with the clinical monitor and as needed, provide them appropriate evidence that the study is being conducted in accordance with the protocol, applicable regulations, and GCP guidelines.

16.6 Quality Control and Quality Assurance

The Sponsor or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, security, and reliability of the study data presented to the Sponsor lies with the investigator generating the data.

The Sponsor or its designee will arrange audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the protocol, standard operating procedures, GCP, and all applicable regulatory requirements. Audits will be independent of and separate from the routine monitoring and quality control functions. Quality assurance procedures will be performed at study sites and during data management to assure that safety and efficacy data are adequate and well documented.

16.7 Protocol Amendment and Protocol Deviation

16.7.1 Protocol Amendment

Amendments to the protocol that entail corrections of typographical errors, clarifications of confusing wording, changes in study personnel, and minor modifications that have no effect on the safety of subjects or the conduct of the study will be classed as administrative amendments and will be submitted to the IEC/IRB for information only. Syneos Health will ensure that acknowledgement is received and filed. Amendments that are classed as substantial amendments must be submitted to the appropriate regulatory authorities and the IECs/IRBs for approval and will not be implemented at sites until such approvals are received, other than in the case of an urgent safety measure.

16.7.2 Protocol Deviations

Should a protocol deviation occur, the Sponsor must be informed as soon as possible. Protocol deviations and/or violations and the reasons they occurred will be included in the clinical study report. Reporting of protocol deviations to the IEC/IRB and in accordance with applicable regulatory authority mandates is an investigator's responsibility.

- All protocol deviations will be tracked in the Clinical Trial Management System. Deviations considered major will be identified as such before study unblinding during medical monitor periodic review.

Major protocol deviations will be tabulated including the frequency and percentage of subjects with each type of deviation by treatment group.

16.8 Ethical Considerations

This study will be conducted in accordance with this protocol, the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the CFR; and in compliance with GCP guidelines.

IECs/IRBs will review and approve this protocol and the ICF. All subjects and/or caregivers (Ukraine only) are required to give written informed consent before participation in the study.

16.9 Financing and Insurance

Before the study commences, the Sponsor (or its designee) and the investigator (or the institution, as applicable) will agree on costs necessary to perform the study. This agreement will be documented in a financial agreement that will be signed by the investigator (or the institution signatory) and the Sponsor (or its designee).

The investigator is required to have adequate current insurance to cover claims for negligence and/or malpractice (US only). The Sponsor will provide no-exclusion insurance coverage for the clinical study as required by national regulations.

16.10 Publication Policy/Disclosure of Data

Both the use of data and the publication policy are detailed within the clinical study agreement. Intellectual property rights (and related matters) generated by the investigator and others performing the clinical study will be subject to the terms of a clinical study agreement that will be agreed between the institution and the Sponsor or their designee. With respect to such rights, the Sponsor or its designee will solely own all rights and interests in any materials, data, and intellectual property rights developed by investigators and others performing the clinical study described in this protocol, subject to the terms of any such agreement. In order to facilitate such ownership, investigators will be required to assign all such inventions either to their institution or directly to the Sponsor or its designee, as will be set forth in the clinical study agreement.

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18 APPENDICES

Appendix 1: Contraception Guidelines

Women of childbearing potential (WOCBP) and men whose sexual partners are WOCBP must use at least 1 highly effective method of contraception during the study and for 7 days after the last dose of study treatment.

A woman is considered to be a WOCBP (fertile) following menarche and until becoming postmenopausal, unless she is permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

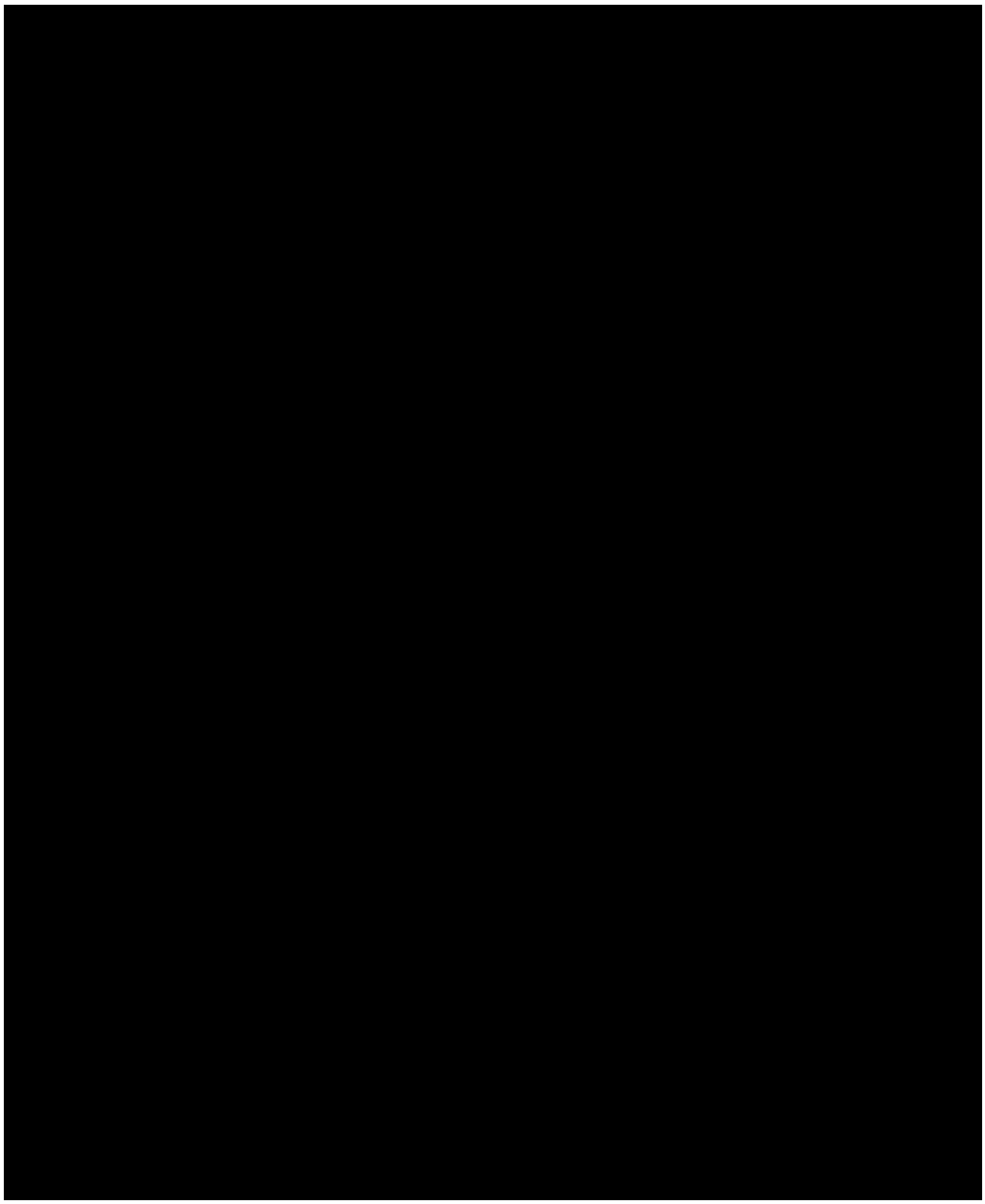
Highly effective methods of contraception are those which have a failure rate of <1% (when implemented consistently and correctly) and include:

- combined (containing estrogen and progestogen) hormonal contraception associated with inhibition of ovulation (administration may be oral, intravaginal, or transdermal)
- progestogen-only hormonal contraception associated with inhibition of ovulation (administration may be oral, injectable, or implantable)
- intrauterine device
- intrauterine hormone-releasing system
- bilateral tubal ligation or occlusion
- vasectomy (provided that the male has a medical assessment of surgical success)
- sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk in relation to the duration of the clinical trial, in line with the preferred and usual lifestyle of the subject)

All subjects will be strongly advised that they (or the female partners of male subjects should not become pregnant while on study treatment or for 7 days after the last dose). A female subject will be advised that she must report immediately to the study site for pregnancy testing and appropriate management in the event that she may be pregnant.

Reference: [HMA] Heads of Medicines Agencies. Clinical Trial Facilitation Group page. Recommendations related to contraception and pregnancy testing in clinical trials. http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf. September 15, 2014. Accessed April 8, 2020.

Appendix 2: Functional Constipation Inquiry



Appendix 3: Alternative Procedures During COVID-19 Pandemic-Related Physical Distancing

The table below (Alternative Schedule of Assessments) outlines the timing of alternative visits procedures and assessments that may be used to replace scheduled on-site study visits during COVID-19 pandemic-related quarantine or mandated physical distancing.

A Home Health Care nurse or the study site staff will visit the subject to complete the scheduled alternate visit. To augment the remote visit, the telemedicine will be used.

Alternative Schedule of Assessments

DAY (± 3d, unless otherwise noted)	56	84	112	140	168	196	224	252	280	308	336	
WEEK	8	12	16	20	24	28	32	36	40	44	48	
VISIT	7R	9R	11R	13R	15R	17R	19R	21R	23R	25R	27R	UNS-R[a]
TYPE OF VISIT	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote	Remote
PROCEDURE												
Urine pregnancy test (WOCBP only) (1),[b]	X	X	X	X	X	X	X	X	X	X	X	X
Urine drugs of abuse and alcohol testing (1),[c]	X	X	X	X	X	X	X	X	X	X	X	X
Body weight, BMI, waist circumference (1),[d]	X	X	X	X	X	X	X	X	X	X	X	X
Blood samples for clinical laboratory tests (1),[e]			X			X			X			
Blood sample for prolactin (1)			X			X			X			
Functional constipation inquiry (2),[f]	X	X	X	X	X	X	X	X	X	X	X	X
Clinical observations (1),[g]	X	X	X	X	X	X	X	X	X	X	X	X
Safety follow up of any AE and/or conmed changes reported by the HHC staff, as needed (2),[h]	X	X	X	X	X	X	X	X	X	X	X	X
PK blood draw (1),[i]		X			X							
PANSS (3),[j]	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS (3),[k]	X	X	X	X	X	X	X	X	X	X	X	X
CGI-S (3)	X	X	X	X	X	X	X	X	X	X	X	X
BARS (3)			X			X			X			X
AIMS (3)			X			X			X			X
KarXT dispensed using MedReady dispenser (1),[l]	X	X	X	X	X	X	X	X	X	X	X	
Subject self-administration of KarXT using AiCure app (1),[l]	X	X	X	X	X	X	X	X	X	X	X	
EMA PRO[m]	X	X	X	X	X	X	X	X	X	X	X	
EMA VLMT[n]	X	X	X	X	X	X	X	X	X	X	X	
Digital biomarkers of schizophrenia [o]	X	X	X	X	X	X	X	X	X	X	X	

Abbreviations: AE = adverse event; AIMS = Abnormal Involuntary Movement scale; BARS = Barnes Akathisia Rating Scale; BMI = body mass index; BP = blood pressure; CGI-S = Clinical Global Impression–Severity scale; C-SSRS = Columbia-Suicide Severity Rating Scale; d = day; EMA = ecological momentary assessment; HR = heart rate; PANSS = Positive and Negative Syndrome Scale; PK = pharmacokinetic; R = remote; UNS = unscheduled visit.

(1) This procedure will be performed either by a Home Health Care nurse or the study site staff.
(2) This procedure will be performed by telemedicine over a telephone or through video chat.
(3) Procedure conducted by telemedicine through video chat only (telephone assessment will not be permitted).

a. Other assessments as needed.
b. A urine pregnancy test for WOCBP should be performed at indicated visits. If a urine pregnancy test is positive, a serum sample should be sent to central laboratory for confirmation of the result.
c. A National Institute on Drug Abuse-5 (NIDA-5) urine drug screen (cannabinoids or marijuana, phencyclidine, amphetamines, opiates, and cocaine) and test for alcohol (breathalyzer or blood alcohol level) will be performed at indicated visits.
d. At the indicated study visits, body weight and waist circumference will be measured and BMI calculated.
e. Refer to Section 0 for individual laboratory tests. For urinalysis, a urine dipstick will be performed locally. In the event of abnormalities, the sample will be sent to the central laboratory for full microscopic urinalysis.
f. Functional constipation inquiry: At specified visits, subjects will be asked whether they have experienced constipation (per the ROME III criteria and Bristol Stool Form Scale; see APPENDIX 2) since the last visit and if yes, whether the constipation required intervention. If the subject answers yes, sites are instructed to ask subjects to provide event date and ensure the event is documented as an AE and treatment is documented as concomitant medication.
g. Clinical observations include collection of vital signs, review of spontaneous AEs, and concomitant medications. These assessments will be performed by a Home Health Care (HHC) nurse and/or site staff visiting the patient at home. Vital signs measurements should be taken at all alternate visits, while the subject is supine and standing after 2 minutes. BP includes systolic and diastolic BP and should be taken in the same arm for the duration of the study whenever possible.
    - Adverse events as reported by subjects or observed by clinical staff. Adverse events occurring after dosing with KarXT in the current study (and resolution) will be recorded in the KAR-008 AE eCRF. One PK blood sample may be drawn if a relevant/significant AE (based on medical judgment) is reported during a scheduled visit or if there is a dose titration or a relevant/significant AE reported during an unscheduled visit (no multiple draws).
    - All medications and other treatments taken by the subject during the study, including those treatments initiated before the start of the study, must be recorded on the KAR-008 eCRF. For any new AEs or concomitant medication reported by the HHC nurse, site staff must follow up with subjects directly via telemedicine over telephone or through video chat and complete a safety follow-up evaluation.
h. For any new AEs or concomitant medication reported by the HHC nurse, site staff must follow up with subjects directly via telemedicine over telephone or through video chat and complete a safety follow-up evaluation.
i. PK blood samples will be collected in the morning before dosing on Days 84, 168, and 364. On these days collection of a single sample before the morning dose is preferred. However, timing of the sample is not mandatory and will not be captured as a protocol deviation if collected after the morning dose (but must be collected on required visit day). Note: In cases of dose reduction, re-escalation, or re-titration, additional PK samples should be collected at 8 and 14 days (+/- 2) post dose change in accordance with the Visits 3 and 4 schedules, unless these additional samples overlap with regularly scheduled PK samples. Otherwise unscheduled visits should be performed to collect these additional samples.
j. It is recommended, if at all possible, that the PANSS assessment should be performed before all the other scale assessments for all visits at which it is performed. The PANSS assessment includes the Marder Factor.
k. The “since last visit” version should be used for C-SSRS administration. At the Unscheduled visit, the C-SSRS should be performed to monitor subjects for suicidality.
l. See Study Operations Manual for details.
m. EMA PRO will be completed by the subject at home on a cellular device 3 times per day for 7 days every 28 days, beginning on Day 29.

n. Cognitive insight will be assessed using the EMA VLMT. The assessment will be completed by the subject at home on a cellular device 1 time per day for 3 days every 28 days beginning on Day 32. Refer to Study Operational Manual for details.
o. Digital biomarkers of schizophrenia will be calculated through completion of a smartphone-based assessment daily by the subject for 3 days collected daily for 3 days every 28 days, beginning on Day 29.

1 FINAL CLINICAL STUDY PROTOCOL

Karuna Therapeutics

Protocol Title: An Open-label Extension Study to Assess the Long-term Safety, Tolerability, and Efficacy of KarXT in Subjects with DSM-5 Schizophrenia

Protocol Number: KAR-008

IND Number:	127471
EudraCT Number:	Not applicable
Name of Investigational Product:	KarXT
Phase of Development:	Phase 3
Indication:	Schizophrenia
Sponsor:	Karuna Therapeutics 33 Arch Street Suite 3110 Boston, MA 02110 Tel: [redacted] Email: [redacted]
Protocol Version:	Version 3.0
Protocol Date:	30 Jun 2021

PROTOCOL APPROVAL SIGNATURES

Protocol Title: An Open-label Extension Study to Assess the Long-term Safety, Tolerability, and Efficacy of KarXT in Subjects with DSM-5 Schizophrenia

Protocol Number: KAR-008

This study will be conducted in compliance with the clinical study protocol (and amendments), International Council for Harmonisation (ICH) guidelines for current Good Clinical Practice (GCP), and applicable regulatory requirements.

Sponsor Signatory

[redacted]
Karuna Therapeutics

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Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 7/2/2021 | 12:58:28 PM PDT
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Karuna Therapeutics

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INVESTIGATOR SIGNATURE PAGE

Protocol Title: An Open-label Extension Study to Assess the Long-term Safety, Tolerability, and Efficacy of KarXT in Subjects with DSM-5 Schizophrenia

Protocol Number: KAR-008

Confidentiality and Current Good Clinical Practice (GCP)/E6(R2) Compliance Statement

- I, the undersigned, have reviewed this protocol (and amendments), including appendices, and I will conduct the study as described in compliance with this protocol (and amendments), and relevant International Council for Harmonisation (ICH) guidelines including GCP and applicable regulatory requirements.
- I am thoroughly familiar with the appropriate use of the KarXT, as described in this protocol and any other information provided by Karuna Therapeutics including, but not limited to, the current investigator's brochure.
- Prior to initiating the trial, I will provide the independent ethics committee (IEC)/institutional review board (IRB) all items subject to review and will obtain a written and dated approval/favorable opinion. Once the protocol has been approved by the IEC/IRB, I will not modify this protocol without obtaining prior approval of Karuna Therapeutics and of the IEC/IRB. I will submit the protocol amendments and/or any informed consent form modifications to Karuna Therapeutics and the IEC/IRB, and approval will be obtained before any amendments are implemented.
- I ensure that all persons or party assisting me with the study are adequately qualified and informed about the Karuna Therapeutics KarXT and of their delegated study-related duties and functions as described in the protocol. I will supervise these delegated persons or parties in the conduct of this trial.
- I ensure that source documents and trial records that include all pertinent observations on each of the site's trial subjects will be attributable, legible, contemporaneous, original, accurate, and complete.
- I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all case report forms, laboratory samples, or source documents forwarded to the Sponsor. Clinical information may be reviewed by the Sponsor or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.
- Information developed in this clinical study may be disclosed by Karuna Therapeutics to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

<Name>

<Title>

_____
Investigator Signature

_____
Date (DD-Mmm-YYYY)

_____
Institution

2 SYNOPSIS

Title of Study:	An Open-label Extension Study to Assess the Long-term Safety, Tolerability, and Efficacy of KarXT in Subjects with DSM-5 Schizophrenia
Protocol Number:	KAR-008
Investigators/Study Sites:	Approximately 30 study sites in the United States and 10 study sites in Ukraine
Phase of Development:	Phase 3
Objective(s):	**Primary Objective:** The primary objective of the study is to assess the long-term safety and tolerability of KarXT in subjects with a Diagnostic and Statistical Manual-Fifth Edition (DSM-5) diagnosis of schizophrenia. **Secondary Objectives:** The secondary objective of this study is to assess the long-term efficacy and evaluate plasma concentrations of xanomeline and trospium after administration of KarXT in adults with a DSM-5 diagnosis of schizophrenia: • To evaluate the reduction in Positive and Negative Syndrome Scale (PANSS) total score • To evaluate the reduction in PANSS positive score • To evaluate the improvement in Clinical Global Impression Severity (CGI-S) results • To evaluate the reduction in PANSS negative score • To evaluate the reduction in PANSS Marder Factor negative symptoms score **Exploratory Objectives:** The exploratory objectives of this study are: • To evaluate cognition with the Cambridge Neuropsychological Test Automated Battery (CANTAB) • To evaluate prolactin levels after administration of KarXT • To evaluate digital biomarkers of schizophrenia • To evaluate ecological momentary assessment administered patient reported outcomes (EMA PRO) in schizophrenia • To evaluate cognitive insight using an EMA administered verbal learning and memory test (EMA VLMT) in schizophrenia
Study Endpoints:	**Primary safety endpoint:** The primary safety endpoint is the incidence of treatment-emergent adverse events (TEAEs) **Secondary safety endpoints:** The secondary safety endpoints of the study are: • Incidence of serious TEAEs • Incidence of TEAEs leading to withdrawal • Secondary efficacy endpoints: • The secondary efficacy endpoints of the study are:

	• Change from baseline in PANSS total score at Week 52 • Change from baseline in PANSS positive score at Week 52 • Change from baseline in PANSS negative score at Week 52 • Change from baseline in PANSS Negative Marder Factor score at Week 52 • Change from baseline in CGI-S score at Week 52 • Percentage of PANSS responders (a 30% change in PANSS total score) at Week 52 **Other Endpoints:** Safety endpoints: The other safety endpoints of the study are: • Spontaneously reported adverse events of special interest (AESIs) • Spontaneously reported procholinergic and anticholinergic symptoms • Change from baseline in Simpson-Angus Rating Scale (SAS) • Change from baseline in Barnes Rating Scale for Akathisia (BARS) • Change from baseline in Abnormal Involuntary Movement Scale (AIMS) • Change from baseline in body weight, body mass index (BMI), waist circumference • Change from baseline in orthostatic vital signs (supine and standing after 2 minutes): blood pressure (systolic and diastolic) and heart rate • Change from baseline in clinical laboratory assessments (hematology, clinical chemistry, coagulation, urinalysis, and drug screen) • Change from baseline in 12-lead electrocardiogram (ECG) • Change from baseline in physical examination • Suicidal ideation scale with the use of Columbia-Suicide Severity Rating Scale (C-SSRS) Pharmacokinetic Endpoint: • Comparison of the plasma concentrations of xanomeline and trospium measured in this study to the plasma concentrations predicted by a population pharmacokinetic (PK) model of studies KAR-007 and KAR-009 Exploratory Endpoints: The exploratory endpoints of the study are: • Change from baseline in cognition measuring core domains of impairment in schizophrenia using CANTAB • Change from baseline in prolactin levels • Observed digital biomarkers of schizophrenia (US only) • Observed EMA PRO in schizophrenia (US only) • Observed cognitive insight using EMA VLMT in schizophrenia (US only)
Study Design:	This is a Phase 3 multicenter, 53-week, outpatient, open-label extension (OLE) study to evaluate the long-term safety, tolerability, and efficacy of KarXT in subjects with DSM-5 schizophrenia who previously completed the treatment period of one of the two Phase 3 double-blind studies,

	KAR-007 or KAR-009. The study consists of a 52-week OLE treatment phase and a 7-day (±3 days) safety follow-up/end-of-study visit after the last KarXT dose for subjects who complete the treatment phase and those who prematurely discontinue from the study. After written informed consent, subjects who have completed the KAR-007 or KAR-009 Phase 3 acute study and received the last dose of the study drug in that trial will be rolled over into the current OLE study. The assessments performed on Visit 10 (Day 35) of studies KAR-007 or KAR-009 will be considered as baseline assessments along with any additional procedures that will be performed on Day 0 of the current study. Any scheduled Day 0 assessments that were not completed on Day 35 of the acute study (KAR-007 or KAR-009) must be completed on Day 0 of the current study. It is preferable that Baseline/Day 0 procedures of the current study be completed on the same day as Day 35 of the acute study after all Visit 10 (Day 35) procedures of the prior study KAR-007 or KAR-009 have been completed. However, with medical monitor approval, an extension of up to 3 days can be granted to complete Baseline/Day 0 procedures. This extension cannot be completed inpatient. With medical monitor approval, participants may be permitted to complete the first 3 days (Visit 1/Day 1 to Visit 2/Day 3) of KAR-008 on the inpatient unit. Twice-daily dosing with KarXT will commence in the morning of Day 1. Subjects who did not complete the full treatment period, or who early terminated study KAR-007 or KAR-009, will not be eligible to enroll in this long-term extension study. Approximately 350 subjects are planned to be enrolled in this study (aged 18 to 65 years) across approximately 30 study sites in the United States and 10 study sites in Ukraine. In this OLE study, all subjects will receive KarXT for up to 52 weeks. Regardless of treatment assignment in the preceding Phase 3 acute study (KAR-007 or KAR-009), all subjects will start on a lead-in dose of KarXT 50/20 (50 mg xanomeline/20 mg trospium) 2 times per day (BID) for the first 2 days (Days 1 and 2), followed by KarXT 100/20 BID for the remainder of Week 1 (Days 3 to 7). At Visit 3 (Day 8), dosing will be titrated upwards to KarXT 125/30 BID unless the subject is continuing to experience adverse events (AEs) from the previous dose of KarXT 100/20 BID. All subjects who are increased to KarXT 125/30 BID, depending on tolerability, will have the option to return to KarXT 100/20 BID. Re-escalation to 125/30 BID or re-titration in cases in which the subject has been off KarXT for a longer period of time (at least a week) is allowed and will require a discussion between the principal investigator and the medical monitor. Additional changes to KarXT dosing (e.g., temporary dose reductions) may be permitted as clinically indicated upon approval by the medical monitor. Beginning after Visit 9/Day 84, interim visits will be completed with flexibility between in-clinic visits, approximately once every 4 weeks. Interim visits will be conducted by telemedicine; however, sites will have the option to schedule on-site interim visits as needed to facilitate subject retention and ensure adherence to study objectives. Additional unscheduled study visits may be conducted as needed.

	A safety follow-up/end-of-study visit (Visit 30/Day 371 ±3 days) will be performed for all subjects after the last dose of KarXT. An Independent Safety Monitoring Committee will be responsible for periodically reviewing the safety data from this study and confirming that the study may continue.
Study Population:	**Inclusion Criteria:** Individuals must meet all of the following criteria to be included in the study: 1. Subject is aged 18 to 65 years, at time of enrollment into the preceding acute study (KAR-007 or KAR-009). 2. Subject is capable of providing informed consent. a. A signed informed consent form must be provided before any study assessments are performed. b. Subject must be fluent in (oral and written) English (United States only) or local language (Ukraine only) to consent. 3. Subject has completed the treatment period on study drug (through Day 35 -2 days) of studies KAR-007 or KAR-009. 4. Subject resides in a stable living situation, in the opinion of the investigator. 5. Subject has an identified, reliable informant/caregiver willing to be able to address some questions related to certain study visits, if needed. An informant/caregiver may not be necessary if the subject has been the patient of the investigator for ≥1 year. 6. Women of childbearing potential (WOCBP) or men whose sexual partners are WOCBP must be willing and able to adhere to the contraception guidelines as defined in Section 8.4.1 and Appendix 1. **Exclusion Criteria:** Subjects will be excluded from the study if 1 or more of the following criteria is/are applicable: 1. Risk for suicidal behavior during the study as determined by the investigator's clinical assessment and C-SSRS as confirmed by the following: a. Subject answers "Yes" to "suicidal ideation" Item 4 (active suicidal ideation with some intent to act, without specific plan) or Item 5 (active suicidal ideation with specific plan and intent) on the C-SSRS. b. Nonsuicidal self-injurious behavior is not exclusionary. 2. Any clinically significant abnormality, including any finding(s) from the physical examination, vital signs, ECG, or laboratory test at the end-of-treatment visit of Studies KAR-007 or KAR-009 that the investigator, in consultation with the medical monitor, would consider to jeopardize the safety of the subject. 3. Female subject is pregnant, breast feeding or planning to become pregnant during the course of the study. 4. If, in the opinion of the investigator (and/or Sponsor), subject is unsuitable for enrollment in the study or subject has any finding that, in the view of the investigator (and/or Sponsor), may compromise the safety of the subject or affect his/her ability to adhere to the protocol visit schedule or fulfill visit requirements.

	5. Subjects with extreme concerns relating to global pandemics such as coronavirus disease 2019 (COVID-19) that preclude study participation. 6. Risk of violent or destructive behavior. 7. Subjects participating in another investigational drug or device trial or planning on participating in another clinical trial during the course of the study.
Planned Sample Size:	Approximately 350 subjects are planned to be enrolled in this study.
Investigational Therapy:	1. Fixed dose KarXT 50/20 BID (50 mg xanomeline/20 mg trospium) oral (Days 1 to 2) 2. Fixed dose KarXT 100/20 BID (100 mg xanomeline/20 mg trospium) oral (Days 3 to 7) 3. Fixed dose KarXT 125/30 BID (125 mg xanomeline/30 mg trospium) oral (Days 8 to 364, if tolerated)
Reference Therapy:	Not applicable.
Treatment Duration:	Total study duration is up to 53 weeks, including a 52-week treatment phase and a 7-day follow-up/end-of-study phase.
Safety assessments:	Spontaneous AEs including AESIs; procholinergic and anticholinergic symptoms, serious AEs (SAEs) and AEs leading to discontinuation of KarXT; SAS; BARS; AIMS; body weight; BMI; waist circumference; orthostatic vital signs; clinical laboratory assessments (hematology, clinical chemistry, coagulation, urinalysis, and drug screen); 12-lead ECG; physical examination; and C-SSRS will be evaluated throughout the study as scheduled.
Efficacy assessments:	PANSS total score, PANSS positive score, PANSS negative score, PANSS Negative Marder Factor score, and CGI-S score will be evaluated at scheduled visits.
Pharmacokinetic assessment:	Blood samples will be collected at scheduled visits for bioanalysis of plasma concentrations of xanomeline and trospium, and will be compared to the plasma concentrations predicted by a population pharmacokinetic (PK) model of studies KAR-007 and KAR-009.
Exploratory assessments	Cognition testing using CANTAB; prolactin levels; digital biomarkers of schizophrenia; EMA PRO and EMA VLMT will be evaluated during scheduled visits or on specified study days.
Statistical Methods and Planned Analyses:	Study Populations: Enrolled population: All subjects who have given informed consent for KAR-008. Safety population: All subjects who receive at least 1 dose of KarXT during the current study will be included in the safety population and will be used in the safety analysis. Modified ITT (mITT) population: All subjects who are enrolled, received at least 1 dose of KarXT during the current study, have a valid PANSS assessment at KAR-008 baseline will be included in the mITT population and will be used in the efficacy analysis. PK population: All subjects who have received at least 1 dose of KarXT and have at least 1 measurable plasma concentration in the current study will be included in the PK population.

	The primary safety endpoint of the study is the incidence of TEAEs. Secondary safety endpoints are the incidence of serious TEAEs and the incidence of TEAEs leading to withdrawal of KarXT. The secondary efficacy endpoints are change from baseline to Week 52 in the PANSS total score, PANSS positive score, PANSS negative score, PANSS Negative Marder Factor score, CGI-S score, and the percentage of PANSS responders at Week 52. The exploratory endpoints of the study are change from baseline in cognition (CANTAB), prolactin levels, digital biomarkers, EMA PRO, and EMA VLMT. Descriptive statistics will be used to provide an overview of the safety and efficacy results. For continuous parameters, descriptive statistics will include n, mean, median, standard deviation, minimum and maximum; For categorical parameters, the number and percentage of subjects in each category will be presented. The denominator for percentages will be based on the number of subjects appropriate for the purposes of analysis. No statistical hypothesis testing will be performed.

3 TABLE OF CONTENTS

3.1 List of In-text Tables

3.2 List of In-text Figures

4 LIST OF ABBREVIATIONS

Abbreviation	Definition
AD	Alzheimer's disease
AE	adverse event
AESI	adverse event of special interest
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
APD	antipsychotic drug
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{0-24}	area under the plasma concentration-time curve from 0 to 24 hours
BACS	Brief Assessment of Cognition in Schizophrenia
BARS	Barnes Akathisia Rating Scale
BID	twice daily
BMI	body mass index
BP	blood pressure
CANTAB	Cambridge Neuropsychological Test Automated Battery
CFR	Code of Federal Regulations
CGI-S	Clinical Global Impression–Severity
C_{max}	maximum plasma concentration
CNS	central nervous system
COVID-19	coronavirus disease 2019
C-SSRS	Columbia-Suicide Severity Rating Scale
DSM-5	Diagnostic and Statistical Manual–Fifth Edition
EDC	electronic data capture
ECG	electrocardiogram
EOS	end of study
EOT	end of treatment
ET	early termination
eCRF	electronic case report form
EMA	Ecological Momentary Assessment
EMAW	Ecological Momentary Assessment Wellness
EPS	extrapyramidal symptoms

Abbreviation	Definition
ET	early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
HIPAA	Health Insurance Portability Accountability Act
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	interactive web response system
IXRS	interactive response system
MCC	microcrystalline cellulose
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini International Neuropsychiatric Interview
mITT	modified intent-to-treat
MMRM	mixed model repeated measures
OLE	open-label extension
PANSS	Positive and Negative Syndrome Scale
PI	principal investigator
PK	pharmacokinetic(s)
PRO	patient reported outcome
SAS	Simpson-Angus Rating Scale
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Simpson Angus Scale
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TID	thrice daily
TK	toxicokinetic
T_{max}	time to maximum plasma concentration

Abbreviation	Definition
ULN	upper limit of normal
US	United States
VAS	visual analog scale
VLMT	Verbal Learning and Memory Test
WOCBP	women of childbearing potential

5 INTRODUCTION

5.1 Background on Schizophrenia

Schizophrenia is a long-term mental disorder involving a breakdown in the relation between thought, emotion, and behavior, and leads to faulty perception, inappropriate actions and feelings, withdrawal from reality and personal relationships into fantasy and delusion, and a sense of mental fragmentation. Symptoms include delusions, hallucination, disorganized speech or behavior, and impaired cognitive ability.[1] The prevalence of schizophrenia is between 0.6% and 1.9% in the United States population.[2] Moreover, a claims analysis has estimated that the annual prevalence of diagnosed schizophrenia in the United States (US) is 5.1 per 1000 lives.[3] It is found equally in males and females, with males usually having an earlier onset of symptoms.[4]

Antipsychotic drugs (APDs) are the mainstay of treatment for schizophrenia.[5] All currently available antipsychotics act through blockage of all or subsets of dopamine receptors in the brain. First-generation APDs include chlorpromazine and haloperidol; treatment with these agents is marked by high rates of parkinsonian extrapyramidal symptoms (EPS) and tardive dyskinesia and they consequently have limited use today. The second-generation agents, that include risperidone, olanzapine, quetiapine, lurasidone, aripiprazole, and lumateperone, tend to have lower levels of EPS or tardive dyskinesia and are currently the most commonly prescribed APD class. However, the second-generation drugs also have problematic side effects that include significant weight gain, metabolic disturbances, sedation, and akathisia.[6, 7, 8] These side effects contribute to poor medication adherence resulting in frequent relapses and hospitalizations.[9, 10] Thus, there is a need for medications for schizophrenia which act through alternative mechanisms.

Central muscarinic receptors have been hypothesized to be therapeutic treatments for schizophrenia based on several converging lines of evidence including both animal and human studies.[11, 12] There are 5 subtypes of muscarinic receptors (M1-M5). The therapeutic effect of central muscarinic receptor agonism is thought to be due to agonism of M1 and M4 receptors in the central nervous system (CNS).[13] However, compounds that agonize M1 and M4 receptors are often not specific enough not to also agonize M2 and M3 receptors outside of the CNS due to the highly conserved allosteric binding sites that the receptors share, leading to adverse events (AEs) related to activation of these peripheral receptors. Thus, any potential benefit of muscarinic agonists in schizophrenia (or other indications such as Alzheimer's disease [AD]) has been outweighed by the occurrence of AEs associated with peripheral cholinergic side effects (nausea, vomiting, diarrhea, sweating, and excess salivation).

5.2 Background on KarXT (Xanomeline Tartrate and Trospium Chloride)

Xanomeline tartrate is a muscarinic-cholinergic receptor agonist. It has agonistic activity at all 5 muscarinic receptors, but preferentially stimulates M_1 and M_4 receptors and binding to M_1 and

M_4 receptors in the CNS, which is thought to be responsible for the drug's potential therapeutic effects (Roth, unpublished data). A recent study reports that xanomeline is a very potent M_4 muscarinic agonist in vivo, measured by various second messenger assays.[14] Xanomeline also enters the brain rapidly achieving a brain to plasma ratio of greater than 10 making it an attractive CNS drug candidate.[15]

Xanomeline does not have any direct binding activity on dopaminergic receptors, suggesting that its mechanism of action is unrelated to direct dopamine involvement.

Previous double-blind, placebo-controlled clinical trials have provided strong evidence that xanomeline has clinically relevant antipsychotic efficacy. In a multicenter outpatient trial in AD (N = 343), 3 doses of xanomeline (up to 225 mg/day) and placebo were assessed for 26 weeks.[16, 17] Significant dose-dependent improvements in psychotic symptoms relative to placebo were observed. Moreover, psychotic symptoms resolved quite rapidly in subjects who were symptomatic at baseline and a dose-dependent reduction in the emergence of psychotic symptoms versus placebo was also observed. In a completer analysis, cognitive improvement was also found suggesting longer treatment intervals may be necessary for cognitive enhancement.[16, 17] In a subsequent small (N = 20) double-blind, placebo-controlled inpatient trial in treatment-resistant subjects with schizophrenia, xanomeline (225 mg/day) demonstrated robust and relatively rapid improvement in psychosis compared to placebo. In addition, improvement in both negative symptoms and cognitive impairment was observed.[18]

In both the AD and schizophrenia trials, as well as in previous healthy volunteer studies, dose-dependent "cholinergic" AEs were also reported, namely vomiting, nausea, diarrhea, sweating, and hypersalivation. These side effects were frequent and, at the higher doses of xanomeline, led to significant rates of discontinuation in the AD studies. This "cholinergic" AE profile curtailed further development of xanomeline as a single agent.

It is believed that the procholinergic AEs associated with xanomeline are mediated by xanomeline's stimulation of *peripheral* rather than *central* muscarinic receptors, which would make these AEs theoretically amenable to counteracting peripheral anticholinergic treatment. Trospium chloride is a peripherally acting muscarinic antagonist which binds to and antagonizes all 5 muscarinic receptor subtypes.[19] It is a commonly used generic drug approved for over 10 years by the US Food and Drug Administration (FDA) and by European authorities to treat overactive bladder and is generally well tolerated.[19] Several human subject studies have demonstrated that trospium does not appreciably cross the blood-brain barrier, consistent with the drug's quaternary ammonium structure.[20]

KarXT is a novel combination of xanomeline tartrate and trospium chloride. Karuna hypothesized that the addition of trospium would mitigate peripheral procholinergic side effects (vomiting, nausea, diarrhea, sweating, and hyper-salivation) and thus provide a strategy to allow xanomeline to be administered and stimulate brain muscarinic receptors with a decreased side effect burden. Phase 1 studies in healthy volunteers of this combination demonstrated that KarXT reduced these side effects by 46% compared to xanomeline alone.[21] Moreover, the

remaining cholinergic AEs were generally mild to moderate in severity and transient in nature, often lasting a few hours without recurrence and were generally single-episode. In general, KarXT was well tolerated in healthy adult volunteers. These encouraging safety data prompted further work to assess KarXT for the treatment of schizophrenia and potentially other CNS disorders.

Karuna has recently completed an adequate and well-controlled, randomized, multi-center Phase 2, placebo-controlled, inpatient clinical trial of acute psychosis with schizophrenia in 182 adult subjects (KAR-004). KarXT demonstrated a statistically significant and clinically meaningful 11.6 point mean reduction in total Positive and Negative Syndrome Scale (PANSS) at 5 weeks compared to placebo ($p < 0.0001$), with statistical separation at each time point assessed (2, 4 and 5 weeks), and also demonstrated good overall safety and tolerability.

The purpose of the current study is to evaluate the long-term safety and tolerability of KarXT (xanomeline 125 mg/trospium 30 mg) administered twice daily (BID) in adult outpatients with Diagnostic and Statistical Manual–Fifth Edition (DSM-5) diagnosis of schizophrenia.

Xanomeline is currently not approved or marketed in any country. Trospium is marketed in the US and other regions of the world for the treatment of overactive bladder.

5.2.1 Nonclinical Studies

The following is a summary of the important nonclinical safety and toxicology studies. More detailed information can be found in the KarXT Investigator's Brochure (IB).

The acute toxicity of xanomeline tartrate was evaluated in mice and rats. All animals were observed for 2 weeks for mortality and clinical signs of intolerance, and then necropsied for gross examinations. In-life findings attributed to the test article included excessive muscarinic-mediated pharmacology, such as excessive salivation, hypoactivity, ataxia, soft stools, exophthalmos, ocular discharge, tremors, and convulsions, with survivors typically appearing normal by Day 3 or Day 4. Gross findings at necropsy were generally unremarkable (eg, gas-distended or mucous-filled gastrointestinal [GI] tracts after oral dosing).

KarXT-301 was a 14-day, repeat dose study of KarXT in rats where relatively high doses of xanomeline and trospium were given, with either xanomeline alone or in combination with trospium. Seven groups of 10 rats/sex/group were administered either vehicle (reverse osmosis water), xanomeline alone at 37, 75, 150, or 300 mg/kg/day (split into BID doses, every 12 hours), or xanomeline/trospium combination doses of 150/200 mg/kg/day or 225/400 mg/kg/day, respectively (split into BID doses, every 12 hours).

Satellite animals were included for the collection of plasma after the first and last doses for the determination of drug concentrations of each parent drug in support of toxicokinetic (TK) assessments.

There was no target-organ toxicity revealed by clinical pathology or by gross or microscopic assessments. All intolerance could be attributed to recognized pharmacology of either test article.

No dose-related ophthalmic observations were noted. Findings were not indicative of specific target organ toxicity. In short, no new hazard was identified.

Clinical observations noted in most animals administered 300 mg/kg/day xanomeline included hypoactivity, clear oral discharge, dilated pupils, irregular or labored respiration, and rough haircoat, among other observations. These findings are generally consistent with the anticipated pharmacology of xanomeline.

Three TK animals in the low-dose combination group died or were euthanized in extremis. It is unclear to what extent the combination treatment effects versus the different handling of these animals (including 3 plasma samplings per animal) contributed to these deaths. If gavage accidents were involved (as happened with some TK animals), then they were not detected at gross necropsy. There was no microscopic evidence of toxicity seen in any toxicity animals in this group or in the higher-dose combination group.

Three toxicology and 3 TK animal deaths (total of 6) occurred in the high-dose combination group. Two toxicology animals had evidence of gavage accidents. For the third, the cause of death was undetermined, and a test article-related effect cannot be ruled out, but esophageal muscular degeneration/regeneration is indicated in some dosing-related trauma. If gavage accidents were involved, then they were not detected at gross necropsy. There was no evidence of target organ microscopic findings in GI tract or any other tissue of any animal, including the early death toxicity animals.

A pharmacodynamics (PD)-mediated reduction in GI motility is consistent with the anti-muscarinic effects of trospium on intestinal musculature. Fecal retention, malabsorption, cessation of eating, dehydration, and rapid deterioration followed with continued dosing. Cessation of dosing in the high-dose combination animals that survived led to rapid recovery, implying the deleterious effects had been PD-related. No effects on food consumption were seen in any xanomeline-alone group. The lack of microscopic findings in the GI tract of any early death or surviving animal implies that the adverse effects were pharmacologically mediated rather than direct target organ toxicity.

Twenty-eight Day Repeat-Dose Studies with Xanomeline in Rats and Monkeys: Rats were fed xanomeline tartrate at 0, 0.05, 0.1, or 0.2% daily and monkeys were fed xanomeline tartrate daily at 0, 5, 12.5, or 30 mg/kg. All animals survived until necropsy. Safety findings in rats included reduced body weight in the high-dose group, increases in gamma-glutamyl-transferase, cholesterol, and bilirubin, slight decreases in triglycerides, bile duct hyperplasia, higher serum potassium (males), and lower serum globulin (females). Findings in monkeys were dose-related and included signs of intolerance such as emesis, salivation, diarrhea, hypoactivity, weight loss, and treatment-related tachycardia in the high-dose animals.

Forty-Day Repeat Dose Study of KarXT in Rats (KarXT-302): Six groups of 15 rats/sex/group were given vehicle, xanomeline alone at 75 or 150 mg/kg/day, trospium alone at 100 mg/kg/day, or xanomeline/trospium combination at doses of 75/50 mg/kg/day or 150/100 mg/kg/day, with

all doses split into BID doses. Satellite rats (TK animals) were included for collection of plasma after the first and last doses to determine concentrations of each drug. Dosing was initially planned to be 90 days, but was terminated after 40 days because of unexpected deaths in the TK animals. No target organ toxicity was seen. Safety findings included pharmacologically mediated constipation in the trospium alone and combination groups, and mild biliary hyperplasia in the high-dose xanomeline-alone and combination groups. There were 4 unscheduled deaths in TK animals; 2 in the high-dose xanomeline-alone group (150 g/kg/day) and 2 in the high-dose combination group (150 mg/kg/day xanomeline plus 100 mg/kg/day trospium). Both xanomeline-only animals had necropsy gross findings of a gavage accident and cause of death could not be determined. All toxicology animals survived to their scheduled sacrifice. The Sponsor considers that the volume depletion and trauma of multiple bleeds (3 per animal) followed by reduced absorption of fluids and nutrients secondary to reduced GI motility with continued BID dosing, explains the greater demise of TK animals relative to toxicity animals.

Based on the results of the 90-day rat toxicology study, oral administration of trospium chloride and xanomeline tartrate alone or in combination to Crl:CD(SD) rats BID (12 hours ±60 minutes apart) at dosage levels of 25 and 50 mg/kg/dose trospium chloride, 37 and 75 mg/kg/dose xanomeline tartrate and a combination of 37/25, 75/25, and 75/50 mg/kg/dose xanomeline tartrate/trospium chloride for a minimum of 90 days resulted in minimal to moderate bile duct hyperplasia in the livers of the xanomeline tartrate and combination (xanomeline tartrate and trospium chloride) group males.

Although there were no notable differences in the incidence of bile duct hyperplasia when comparing the single vs combination groups, there was an increased severity observed in the combination group males (specifically the 75/25 and 75/50 mg/kg/dose combination group males) when compared to the xanomeline tartrate group males at the terminal euthanasia. The bile duct hyperplasia was considered adverse in the high-dose xanomeline tartrate group males and in the 75/25 and 75/50 mg/kg/dose combination group males due to instances of moderate severity. Therefore, the no-observed-adverse-effect level was considered to be 50 mg/kg/dose for trospium chloride, 37 mg/kg/dose for xanomeline tartrate, and 37/25 mg/kg/dose for the combination of xanomeline tartrate/trospium chloride. At these doses for males, mean plasma AUC_{0-24} values were 27,700 pg•hr/mL for trospium, 146,000 pg•hr/mL for xanomeline, and 4510 + 111,000 pg•hr/mL for trospium + xanomeline, respectively, on Day 91.

At these doses for females, mean plasma AUC_{0-24} values were 9230 pg•hr/mL for trospium, 267,000 pg•hr/mL for xanomeline, and 16,700 + 171,000 pg•hr/mL for trospium + xanomeline, respectively, on Day 91. The absence of bile duct hyperplasia in females cannot be explained from differences in drug exposure. At the recovery euthanasia, bile duct hyperplasia was still present, but was limited to minimal severity and there was a decreased incidence in both the xanomeline tartrate and combination group males. There was also no notable difference in severity between the single vs combination groups at the recovery euthanasia. Given the decreased incidence/severity, in combination with the improved histologic appearance of bile

ducts at the recovery euthanasia (ie, smaller/flattened epithelium, non-inflammatory, and an absence of portal bridging), changes at the recovery euthanasia were consistent with a partial resolution of bile duct hyperplasia. With an absence of correlating serum liver enzyme elevations, bile acid alterations or hepatocellular degeneration, necrosis or regeneration, and with the apparent reversibility following cessation of treatment, these findings appear to have been tolerable by the affected animals. Therefore, the maximum tolerated dose was considered to be 50 mg/kg/dose for trospium chloride, 75 mg/kg/dose for xanomeline tartrate, and 75/50 mg/kg/dose for the combination of xanomeline tartrate/trospium chloride.

For males, corresponding mean plasma AUC_{0-24} values were 27,700 pg•hr/mL for trospium, 822,000 pg•hr/mL for xanomeline, and 133,000 + 276,000 pg•hr/mL for trospium + xanomeline, respectively, on Day 91. For females, corresponding mean plasma AUC_{0-24} values were 9230 pg•hr/mL for trospium, 2,090,000 pg•hr/mL for xanomeline, and 17,600 + 950,000 pg•hr/mL for trospium + xanomeline, respectively, on Day 91.

In summary, no new "combination" findings were discovered; toxicology studies revealed the familiar exaggerations of systemic and CNS muscarinic effects that had previously been seen with xanomeline or trospium at high doses. Target organ findings with xanomeline alone were limited to biliary hyperplasia in the 28-day rat study but not the 28-day or 12-month monkey study, though similar findings were described in a 6-month monkey study. With KarXT, biliary hyperplasia was not observed in the 14-day rat study but was reported in the 40-day rat study. Notably, these hyperplastic findings are not thought to represent pre-neoplastic lesions, because they were of low severity; no fibrosis or associated hepatocellular changes, and no significant effects were seen on hepatobiliary-related serum chemistry.

5.2.2 Completed Clinical Studies

Refer to the IB for complete information regarding previous clinical studies conducted with xanomeline by Eli Lilly, and studies KAR-001, KAR-002, KAR-003 and KAR-004 conducted by Karuna Therapeutics using xanomeline with trospium.

To date, more than 840 subjects or volunteers have been exposed to xanomeline tartrate (oral formulation, either alone, in combination with trospium, or as the combination drug KarXT) in 19 completed clinical studies conducted either by Eli Lilly or Karuna Therapeutics, some for as long as 3 years. In those studies, significant improvements in cognition and reduced psychotic symptoms were observed.

A study of xanomeline monotherapy in subjects with schizophrenia was reported in 2008.[18] In this pilot study, the effects of xanomeline were examined in 20 schizophrenia subjects utilizing a double-blind, placebo-controlled, 4-week study design. Subjects treated with xanomeline did significantly better than subjects in the placebo group on Brief Psychiatric Rating Scale total scores and PANSS total scores (ie, 24-point change over placebo, $p = 0.04$). In the cognitive test battery, subjects in the xanomeline group showed improvements relative to placebo in some of the cognitive domains of verbal learning and short-term memory function. These studies

demonstrated the potential for xanomeline as a treatment for psychosis and cognition across multiple subject populations.

Study H2Q-EW-E001, conducted by Eli Lilly, had 36 male healthy volunteers in 4 groups of 9, who were administered escalating single doses of xanomeline tartrate in increments of 1, 5, 10, 25, 50, 75, 100 and 150 mg. Each group took 2 ascending doses of xanomeline tartrate and 1 dose of placebo in a single subject blind manner. There were no serious AEs (SAEs). Adverse events included watery diarrhea, nausea, dizziness, sweating, shivering, mild disorientation, increased blood pressure (BP), increase(s) in sitting and standing heart rate, slight increase in supine systolic BP, and postural hypotension.

The clinical experience with KarXT initiated by Karuna Therapeutics to date includes 3 completed Phase 1, clinical pharmacology studies in healthy volunteers (KAR-001, KAR-002, and KAR-003) and one completed Phase 2 study (KAR-004) in adult inpatients with DSM-5 schizophrenia.

The first study conducted by Karuna, KAR-001 was a Phase 1, double-blind, randomized, multiple-dose, pilot study comparing xanomeline administered alone to xanomeline administered in combination with trospium chloride in normal healthy volunteers. This study consisted of 2 arms, in which xanomeline was administered three times daily (TID), alone, at a total daily dose of 225 mg in 1 arm, and the second arm received the same dose of xanomeline in combination with trospium chloride 20 mg administered BID, a total daily dose of 40 mg. Subjects were treated for 7 days. The goal was to determine whether this dosing regimen would reduce the cholinergic side effects of xanomeline by co-administration of the muscarinic antagonist, trospium.

Overall, treatment with xanomeline 225 mg daily + trospium 40 mg daily administered over 7 days was considered safe and well tolerated. The results of key and supportive endpoints showed a numerical reduction (although not statistically significant) in visual analog scale (VAS) scores for cholinergic events for the xanomeline + trospium treatment arm compared to the xanomeline-alone treatment arm. Specifically, consistent numerical reduction in VAS scores for the xanomeline + trospium treatment arm was observed for the supportive endpoints of maximum weekly individual VAS scores and mean daily maximum composite VAS scores.

Results of the clinician-administered scales were supportive of a reduction in vomiting, feelings of nausea, excess salivation, and sweating that interfered with daily activities in the xanomeline + trospium treatment arm compared to the xanomeline-alone treatment arm.

There were no meaningful differences between treatment groups in heart rate, resting BP, orthostatic BP or any electrocardiogram (ECG) parameters including QT. A small subset of subjects in both treatment arms had transient increases in heart rate and orthostatic BP changes which may have contributed to syncope and postural dizziness in those subjects. Two subjects (both in the xanomeline-alone arm) experienced syncope. The incidence of orthostatic AEs in the KarXT group was approximately one-half that of subjects in the xanomeline-alone group.

The most commonly reported treatment-emergent AEs (TEAEs) in KAR-001 (≥20% of subjects in either treatment arm) were hyperhidrosis, salivary hypersecretion, nausea, dizziness postural, and diarrhea. Subject incidences of these 5 TEAEs was higher in the xanomeline-alone treatment arm (61.8%) compared to the xanomeline + trospium treatment arm (34.3%).

Overall, treatment with xanomeline 225 mg combined with trospium chloride 40 mg administered over 7 days was considered safe and well tolerated. The observed side effect profile was consistent with the known safety profile of xanomeline and trospium chloride. The incidence of TEAEs and cholinergic TEAEs was lower in the xanomeline + trospium treatment arm compared to the xanomeline-alone treatment arm.

Study KAR-002 was a Phase 1, double-blind, randomized, multiple-dose adaptive design pilot study to evaluate the safety and tolerability of KarXT in normal healthy volunteers. Subjects received either 100 mg xanomeline + 20 mg trospium BID or placebo. The first cohort of this study was stopped after 1.5 days when the FDA put the program on hold due to a preliminary rat finding in the 14-day study. This study used a new formulation of KarXT in which xanomeline and trospium were combined into a single dose form and given BID. Safety findings included an increase in orthostatic complaints. Caution should be used in drawing conclusions from this study, as subjects did not have time to reach steady state plasma levels from dosing, as only 3 doses were given.

Study KAR-003 was a Phase 1, double-blind, randomized, multiple-dose, adaptive design, inpatient pilot study to evaluate the safety and tolerability of KarXT in normal healthy volunteers. The primary objective of this study was to assess the safety and tolerability of 7 days of daily administration of KarXT at various dose combinations, administered BID. Subjects received either KarXT or placebo (3:1 ratio). All subjects on KarXT received 2 days of 50 mg xanomeline + 20 mg trospium BID, and then increased to different doses for Days 3 to 7. This study also used the new formulation of KarXT in which xanomeline and trospium were combined into a single dosage form and given BID.

There was a relatively high degree of variability in xanomeline and trospium exposures between individuals in all cohorts, which is consistent with previous results with KarXT, xanomeline-alone, and trospium-alone. Peak plasma concentrations were observed at a median time of 2.0 hours for xanomeline and 1.0 hour for trospium across all treatment groups and study days.

Although there was insufficient data to draw a definitive conclusion regarding the impact of trospium on the pharmacokinetics (PK) and bioavailability of xanomeline, or the impact of xanomeline on the pharmacokinetics and bioavailability of trospium, the PK results suggest that neither drug had a meaningful impact on the PK behavior of the other drug.

During the 2-day lead-in phase, the most common AEs (≥20% of subjects) when all the subjects completed dosing were dry mouth, nausea, and constipation. For the treatment groups that completed dosing, although the incidence of TEAEs was lower in the KarXT 100/20 BID

(66.7%) group compared to KarXT 125/40 group (88.9%), the incidence of cholinergic TEAEs (nausea, vomiting, diarrhea, sweating, and excess salivation) was similar between the 2 groups. The most commonly reported TEAEs (≥20% of subjects in either treatment group) in these groups were dizziness, nausea, dry mouth, headache, vomiting, dyspepsia, somnolence, vision blurred, and dysuria. For the treatment groups that did not complete dosing (KarXT 150/20 BID group and KarXT 150/40 BID group), the cholinergic TEAEs were generally higher compared to the treatment groups that completed dosing.

Overall, anticholinergic TEAEs appeared to occur primarily in the treatment groups that were dosed with 40 mg trospium BID (KarXT 150/40 BID and KarXT 125/40 BID groups), particularly when paired with 125 mg xanomeline BID, suggesting to consider slightly lowering the trospium dose from 40 mg BID in future studies. All TEAEs were mild or moderate in severity, and there were no SAEs or deaths. Treatment-emergent AEs were primarily cholinergic or orthostatic (and a few anticholinergic). Doses of 100 mg and 125 mg BID of xanomeline were well tolerated when paired with 20 mg and 40 mg BID of trospium, respectively. The safety and tolerability profile of KarXT 100/20 BID and KarXT 125/40 BID was acceptable and supports further evaluation at similar doses in future studies. Doses of KarXT 150/20 BID and 150/40 BID were not well tolerated in this study. A pairing of 150 mg xanomeline with 40 mg trospium appeared to be better tolerated than 150/20, but some subjects still experienced tolerability issues.

Study KAR-004 was a Phase 2 randomized, double-blinded study to assess the safety, tolerability, and efficacy of KarXT in adults with DSM-5 schizophrenia, hospitalized with acute psychosis. The primary objective of the study was to assess the efficacy of KarXT (125/30 BID) versus placebo in reducing PANSS total scores in adult inpatients with a DSM-5 diagnosis of schizophrenia. Subjects received either KarXT or placebo (1:1 ratio) for a treatment period of 5 weeks. All subjects on KarXT received a lead-in dose of KarXT 50/20 BID for the first 2 days followed by KarXT 100/20 BID on Days 3 to 7. On Day 8, dosing was titrated upwards to KarXT 125/30 BID unless the subject was continuing to experience AEs from a previous dose increase of 100/20 BID.

A total of 182 subjects were enrolled and randomized (92 placebo; 90 KarXT). Of these subjects, 170 (87 [94.6%] placebo; 83 [92.2%] KarXT) received at least one dose of study drug and had at least one post-baseline PANSS assessment (Modified Intent to Treat population used for the efficacy analyses). Discontinuation rates were similar between the 2 treatment groups; 37 subjects discontinued the study early (19 [20.7%] placebo; 18 [20.0%] KarXT). The most common reason for early discontinuation was consent withdrawn (14 [15.2%] placebo; 14 [15.6%] KarXT) followed by Adverse Event (2 [2.2%] placebo; 3 [3.3%] KarXT).

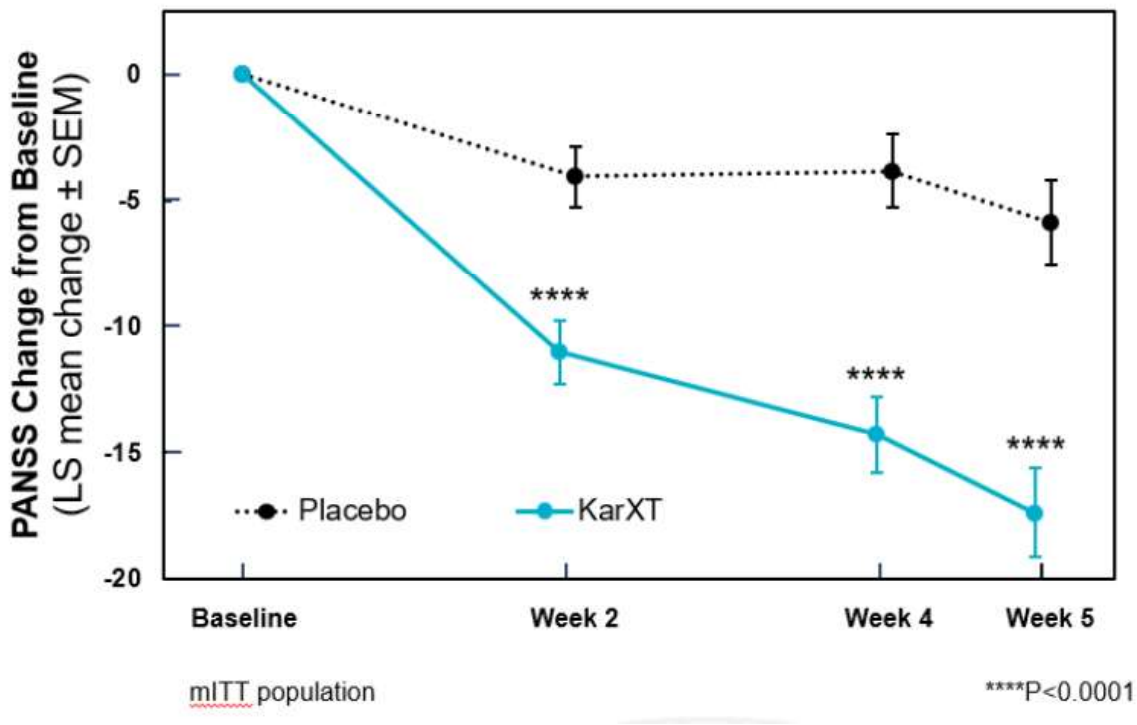
Treatment-emergent adverse events (TEAE) were reported in 43.3% of subjects in the placebo group and 53.9% of subjects in the KarXT group. The most commonly reported TEAEs were constipation, nausea, dry mouth, dyspepsia, and vomiting, and were more common (≥ 5% higher or twice that of placebo) in the KarXT group than in the placebo group.

There were 27.8% and 42.7% of subjects in the placebo and KarXT groups, respectively, who experienced at least 1 TEAE related to study drug. The most commonly reported study drug related TEAEs for the placebo and KarXT total groups were nausea, constipation, dry mouth, dyspepsia, and vomiting and were more common (≥ 5% higher or twice that of placebo) in the KarXT group than in the placebo group. The majority of the reported TEAEs were mild (27.8% placebo; 36.0% KarXT) or moderate (14.4% placebo; 16.9% KarXT) in severity. Two severe TEAEs were reported during the study. One subject in the placebo group had a severe TEAE of worsening schizophrenia symptoms, and 1 subject in the KarXT high dose group had a severe event of increased psychosis which was reported as an SAE possibly related to KarXT by the investigator. There were no other SAEs reported during the study and there were no deaths during the study.

The pattern and course of safety findings in KAR-004 were consistent with the known safety profile from earlier studies of both xanomeline monotherapy and xanomeline combined with trospium (KarXT). Even though the qualitative AE profile was consistent with earlier Phase 1 PK/safety studies in healthy volunteers, the relative tolerability burden was lower in the current study of schizophrenia patients receiving KarXT than in the healthy volunteers. In addition, the safety and tolerability of KarXT was favorable and notably free of many common side effects associated with current antipsychotic drugs.

KarXT demonstrated statistically significant and clinically meaningful reduction in total PANSS score at all time points over 5 weeks compared to placebo (Figure 1). The primary efficacy endpoint result for the study (change from baseline (CFB) in PANSS total score between the placebo group and the KarXT group at Visit 9/Week 5) showed a statistically significant decrease in PANSS total score ($p<0.0001$). The statistically significant difference in CFB between the treatment groups was there at Visit 6/Week 2 ($p<0.0001$) and continued to Visit 8/Week 4 and Visit 9/Week 5. Overall, the decrease from baseline in PANSS total score for the KarXT group was statistically significantly greater compared to the placebo group by treatment group for Visits 6, 8, and 9 ($p<0.0001$).

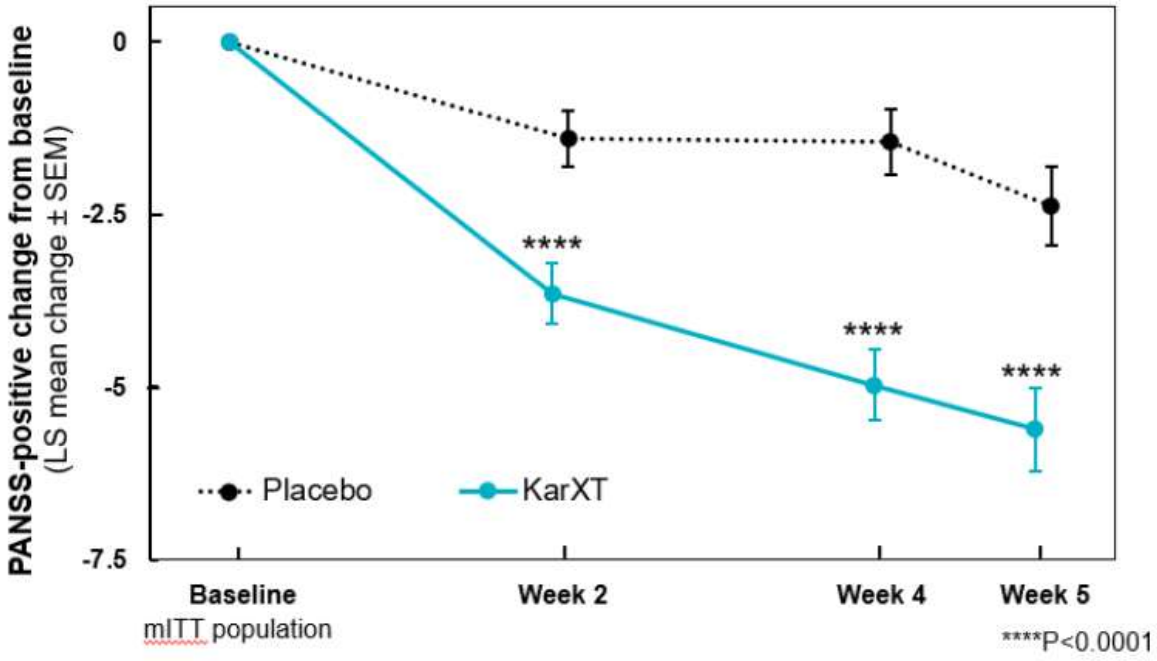
Figure 1. Change from Baseline in PANSS Total Scores (KAR-004)



Abbreviations: LS = least squares; mITT = modified intent-to-treat; PANSS = Positive and Negative Syndrome Scale; SEM = standard error of the mean.

A significant reduction in the secondary endpoint of PANSS-positive scores was observed ($p<0.0001$) at Week 5 as well as the 2 earlier time points (ie, Weeks 2 and 4; see Figure 2).

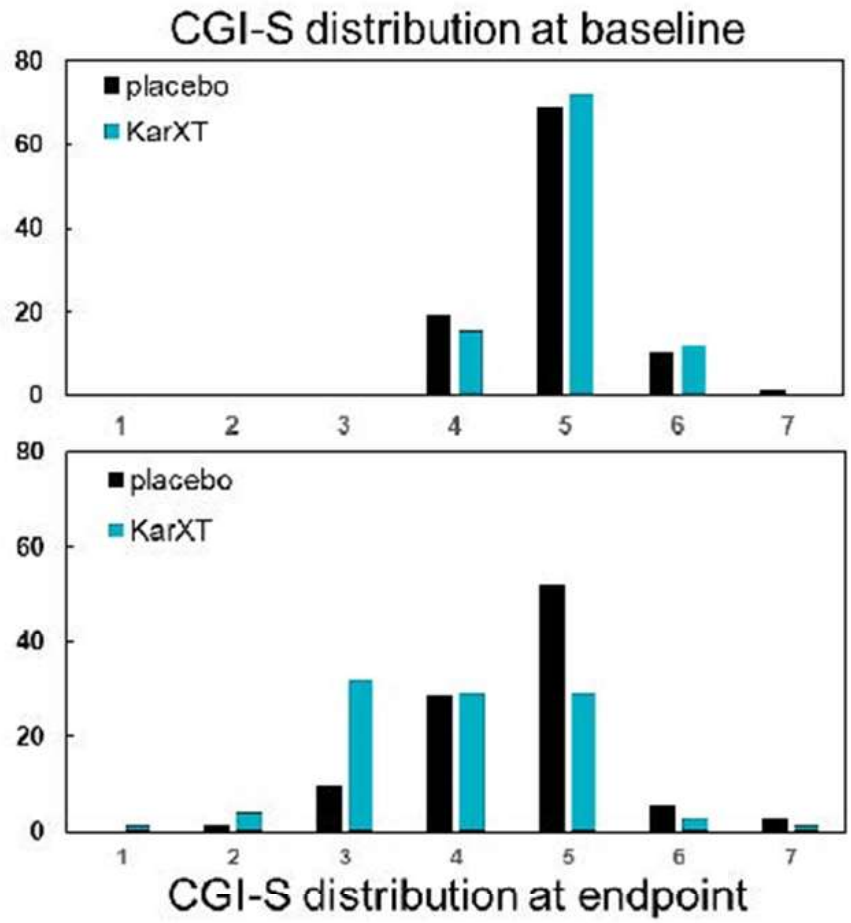
Figure 2. Change from Baseline in PANSS-Positive Scores (KAR-004)



Abbreviations: LS = least squares; mITT = modified intent-to-treat; PANSS = Positive and Negative Syndrome Scale; SEM = standard error of the mean.

As regards the Clinical Global Impression – Severity of Illness (CGI-S), subjects in the KarXT group overall significantly improved in ratings compared to placebo, with a p-value of <0.001 at Week 5. At Week 5, 8% of placebo subjects improved (decreased) their CGI-S ratings at least 2 levels versus 28.9% of KarXT subjects (see Figure 3).

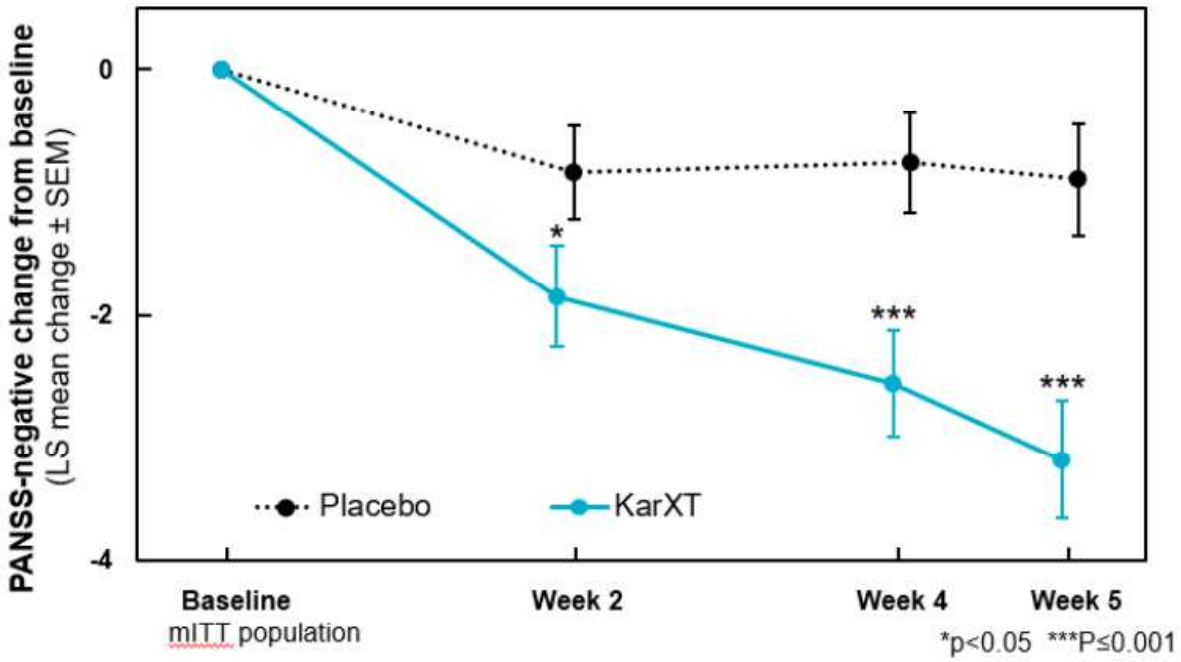
Figure 3. Change from Baseline in CGI-S (KAR-004)



Abbreviation: CGI-S = Clinical Global Impression–Severity.

A statistically significant reduction in the secondary endpoint of PANSS-negative score was observed ($p<0.001$) at Week 5. Overall, the changes in the KarXT group were statistically significantly greater compared to the placebo group at Visits 6, 8, and 9 ($p<0.001$). The least square mean improvement for the placebo group was 1.32 points at Week 5 (Visit 9) and the mean improvement for the KarXT group was 3.85 points leading to a mean difference of 2.53 points at Week 5 (Visit 9; see Figure 4).

Figure 4. Change from Baseline in PANSS-Negative Scores (KAR-004)



Abbreviations: LS = least squares; mITT = modified intent-to-treat; PANSS = Positive and Negative Syndrome Scale; SEM = standard error of the mean.

The overall safety/tolerability data were also fairly unambiguous; among the highlights:

- The overall discontinuation rate on KarXT was 20%, similar to placebo (21%). The number of discontinuations due to TEAEs was equal in the KarXT and placebo arms (N = 2 in each group)
- The dose escalation rate on KarXT was high and similar to placebo:
  - 91% of KarXT subjects escalated to 125/30 KarXT (vs 97% on placebo)
  - 4% percent de-escalated back to 100/20 KarXT dose (vs 1% on placebo)
- The overall TEAE rate on KarXT was 54% vs 43% on placebo:
  - The most common TEAEs were constipation, nausea, dry mouth, dyspepsia, and vomiting. None of these TEAEs were severe and none led to discontinuations
  - One SAE occurred in the study (the subject was on KarXT): the subject discontinued treatment and subsequently sought hospital care for worsening psychosis, meeting the regulatory definition of an SAE.
  - No syncope or mean changes in BP were seen

  - A 5.5 bpm peak mean placebo adjusted resting heart rate increase with a downward trend after Week 2 was seen
  - One subject (on KarXT) was discontinued due to an elevated gamma-glutamyl transpeptidase (GGT)
  - There were no new safety findings associated with KarXT that have not been observed with either xanomeline alone or trospium alone in previous trials

- KarXT did not show evidence of many of the kinds of AEs that often occur in currently available antipsychotics for the treatment of schizophrenia
- The rates of the following AEs were similar for KarXT and placebo: somnolence, weight gain, and EPS
- Overall, the KAR-004 results confirm and extend the antipsychotic benefit of xanomeline observed in past studies of xanomeline alone and the well tolerated nature of KarXT. KAR-004 results support the continued development of KarXT into Phase 3 trials.

Two randomized, double-blind, placebo-controlled Phase 3 trials (KAR-007 and KAR-009) are planned in which the subjects will be exposed to either KarXT or placebo (1:1) for a period of up to 5 weeks. Subjects who complete either of these 2 studies will be eligible to roll over into this long-term open-label study.

5.3 Clinical Risks/Benefits of KarXT and Study Rationale

The risks and benefits of KarXT in humans are not fully known. KarXT is a fixed dose combination of xanomeline and trospium.

The available clinical trial data indicate that KarXT has robust efficacy and a favorable safety profile that appears unique compared to all available APDs. Most of these clinical data were generated by subjects who were either “institutionalized” or studied in an “inpatient” hospital setting. Treatment with KarXT is not associated with weight gain, sedation, or meaningful EPS changes. In contrast, these serious side-effects pose a significant risk with other APD treatments for schizophrenia and can lead to discontinuation of treatment and significant morbidity. A Phase 2 registration quality pivotal trial in 182 subjects met the primary endpoint with the PANSS total score showing a 11.6 point mean improvement compared to placebo with a highly significant ($p < 0.0001$) separation from placebo (-17.4 KarXT vs. -5.9 placebo) at Week 5. KarXT, as compared to placebo, demonstrated highly significant reduction in PANSS total scores ($p < 0.0001$) at all post randomization time points (Weeks 2, 4 and, 5) with a calculated effects size (Cohen’s d) of 0.75. KarXT, as compared to placebo, demonstrated significant improvement at all post randomization time points for PANSS positive symptom subscores, PANSS negative symptom subscores, PANSS Marder Factor negative symptom subscores, and CGI-S scores.

Over 840 subjects or volunteers have been exposed to xanomeline tartrate (oral formulation; either alone, in combination with trospium, or as the combination drug KarXT) in clinical studies. These early clinical studies, as well as nonclinical pharmacology and toxicology studies, have not revealed any specific contraindications to the use of xanomeline. The most common side effects/symptoms are the cholinergic related effects: nausea, vomiting, excess salivation, excess sweating, and diarrhea. In addition, subjects treated with xanomeline alone have reported both syncope and orthostatic dizziness. The addition of trospium decreases the peripheral cholinergic effect of xanomeline creating a better tolerated therapy. In addition, a titration phase also increases the tolerability of KarXT.

Trospium chloride has been marketed in the US for 12 years. The most frequently reported AEs reported in pivotal trials were dry mouth, constipation, abdominal pain, headache, urinary retention, and abnormal vision and accommodation. For additional information, the package insert for trospium chloride tablets for oral use can be found in the IB.

In a Phase 2 (KAR-004) clinical study, KarXT (100/20 and 125/30) significantly reduced the symptoms of schizophrenia in subjects with acute psychosis after treatment for 28 days. KarXT also showed an acceptable safety profile with the most common TEAEs being constipation, nausea, dry mouth, dyspepsia, and vomiting. All the reported TEAEs were mild or moderate in intensity. One SAE (psychotic disorder) was reported by a single subject and no deaths were reported in the study. KarXT was generally well-tolerated and found to be safe in this patient population.

KarXT represents a novel approach to the treatment of patients with schizophrenia that will provide an important and meaningful alternative to current therapies. The current tolerability and AE profile and the efficacy of KarXT justify further development of KarXT in this patient population by advancing to Phase 3 trials. Two such Phase 3 trials (KAR-007 and KAR-009) are planned where the subjects will receive the study drug (KarXT or placebo) for 5 weeks.

In the current study, regardless of treatment assignment in the preceding Phase 3 study (KAR-007 or KAR-009), all subjects will receive KarXT for a period of approximately 52 weeks with the primary objective of assessing the long-term safety and tolerability profile of KarXT in an out-patient setting. All subjects will start with a lead-in dose of KarXT 50/20 BID for Days 1 to 2 and then the dose will be titrated to 100/20 BID for Days 3 to 7, allowing the subject to adjust to KarXT before receiving a higher dose of 125/30 BID starting on Visit 3 (Day 8), unless the subject is continuing to experience AEs from the previous dose increase of KarXT 100/20 BID. All subjects who are increased to KarXT 125/30 BID, depending on tolerability, will have the option to return to KarXT 100/20 BID. Re-escalation to 125/30 BID or re-titration in cases where subject has been off KarXT for a longer period of time (at least a week) is allowed and will require a discussion between the principal investigator (PI) and the medical monitor.

Dosing will occur every 12 ±4.5 hours each day, during waking hours. KarXT should be dosed on an empty stomach (ie, at least 1 hour before a meal or 2 to 3 hours after a meal).

The current study is designed to demonstrate that long-term treatment with KarXT in adult schizophrenia subjects is safe and tolerable.

6 STUDY OBJECTIVES AND ENDPOINTS

6.1 Study Objectives

6.1.1 Primary Objective

The primary objective of the study is to assess the long-term safety and tolerability of KarXT in subjects with a DSM-5 diagnosis of schizophrenia.

6.1.2 Secondary Objectives

The secondary objective of this study is to assess the long-term efficacy and evaluate plasma concentrations of xanomeline and trospium after administration of KarXT in adults with a DSM-5 diagnosis of schizophrenia:

- To evaluate the reduction in PANSS total score
- To evaluate the reduction of PANSS positive score
- To evaluate the improvement in Clinical Global Impression Severity (CGI-S) results
- To evaluate the reduction of PANSS negative score
- To evaluate the reduction of PANSS Marder Factor negative symptoms score

6.1.3 Exploratory Objectives

The exploratory objectives of this study are:

- To evaluate cognition with the Cambridge Neuropsychological Test Automated Battery (CANTAB)
- To evaluate prolactin levels after administration of KarXT
- To evaluate digital biomarkers of schizophrenia (US only)
- To evaluate ecological momentary assessment administered patient reported outcomes (EMA PRO) in schizophrenia (US only)
- To evaluate cognitive insight using an EMA administered verbal learning and memory test (EMA VLMT) in schizophrenia (US only)

6.2 Study Endpoints

6.2.1 Primary Safety Endpoint

The primary safety endpoint of this study is the incidence of treatment-emergent AEs (TEAE).

6.2.2 Secondary Endpoints

6.2.2.1 Safety Endpoints

The secondary safety endpoints of this study are:

- Incidence of serious TEAEs

- Incidence of TEAEs leading to withdrawal

6.2.2.2 Efficacy Endpoints

The secondary efficacy endpoints of this study are:

- Change from baseline in PANSS total score at Week 52
- Change from baseline in PANSS positive score at Week 52
- Change from baseline in PANSS negative score at Week 52
- Change from baseline in PANSS Negative Marder Factor score at Week 52
- Change from baseline in CGI-S score at Week 52
- Percentage of PANSS responders (a 30% change in PANSS total score) at Week 52

6.2.3 Other Endpoints

6.2.3.1 Safety Endpoints

- Spontaneously reported adverse events of special interest (AESIs)
- Spontaneously reported procholinergic and anticholinergic symptoms
- Change from baseline in Simpson-Angus Rating Scale (SAS)
- Change from baseline in Barnes Rating Scale for Akathisia (BARS)
- Change from baseline in Abnormal Involuntary Movement Scale (AIMS)
- Change from baseline in body weight, body mass index (BMI), waist circumference
- Change from baseline in orthostatic vital signs (supine and standing after 2 minutes): BP (systolic and diastolic) and heart rate
- Change from baseline in clinical laboratory assessments (hematology, clinical chemistry, coagulation, urinalysis, and drug screen)
- Change from baseline in 12-lead ECG
- Change from baseline in physical examination
- Suicidal ideation scale with the use of Columbia-Suicide Severity Rating Scale (C-SSRS)

6.2.3.2 Pharmacokinetic Endpoint

- Comparison of the plasma concentrations of xanomeline and trospium measured in this study to the plasma concentrations predicted by a population pharmacokinetic (PK) model of studies KAR-007 and KAR-009

6.2.3.3 Exploratory Endpoints

The exploratory endpoints of this study are:

- Change from baseline in cognition measuring core domains of impairment in schizophrenia using CANTAB

- Change from baseline in prolactin levels
- Observed digital biomarkers of schizophrenia (US only)
- Observed ecological momentary assessment administered patient reported outcomes (EMA PRO) in schizophrenia (US only)
- Observed cognitive insight using an EMA administered verbal learning and memory test (EMA VLMT) in schizophrenia (US only)

7 INVESTIGATIONAL PLAN

7.1 Description of Overall Study Design and Plan

This is a Phase 3 multicenter, 53-week, outpatient, open-label extension (OLE) study to evaluate the long-term safety, tolerability, and efficacy of KarXT in subjects with DSM-5 schizophrenia who previously completed the treatment period of one of the two Phase 3 double-blind studies, KAR-007 or KAR-009. The study consists of a 52-week OLE treatment phase and a 7-day (±3 days) follow-up/end-of-study (EOS) visit after the last KarXT dose for subjects who complete the treatment phase and those who prematurely discontinue from the study.

After written informed consent, subjects who have completed either the KAR-007 or KAR-009 Phase 3 acute study and received the last dose of the study drug in that trial will be rolled over into the current OLE study. The assessments performed on Visit 10 (Day 35) of studies KAR-007 or KAR-009 will be considered as baseline assessments along with any additional procedures that will be performed on Day 0 of the current study. Any scheduled Day 0 assessments that were not completed on Day 35 of the acute study (KAR-007 or KAR-009) must be completed on Day 0 of the current study.

It is preferable that Baseline/Day 0 procedures of the current study be completed on the same day as Day 35 of the acute study after all Visit 10 (Day 35) procedures of the prior study KAR-007 or KAR-009 have been completed. However, with medical monitor approval, an extension of up to 3 days can be granted to complete Baseline/Day 0 procedures. This extension cannot be completed inpatient.

With medical monitor approval, participants may be permitted to complete the first 3 days (Visit 1/Day 1 to Visit 2/Day 3) of KAR-008 on the inpatient unit.

Subjects who did not complete the full treatment period, or who early terminated studies KAR--007 or KAR--009, will not be eligible to enroll in this long-term extension study.

Approximately 350 subjects are planned to be enrolled in this study (aged 18 to 65 years at time of enrollment into the preceding acute study) across approximately 30 study sites in the United States and 10 study sites in Ukraine.

In this OLE study, all subjects will receive KarXT for up to 52 weeks. Regardless of treatment assignment in the preceding Phase 3 acute study (KAR-007 or KAR-009), all subjects will start on a lead-in dose of KarXT 50/20 BID for the first 2 days (Days 1 and 2), followed by KarXT 100/20 BID for the remainder of Week 1 (Days 3 to 7). On Visit 3 (Day 8), dosing will be titrated upwards to KarXT 125/30 BID unless the subject is continuing to experience AEs from the previous dose of KarXT 100/20 BID. All subjects who are increased to KarXT 125/30 BID, depending on tolerability, will have the option to return to KarXT 100/20 BID for the remainder of the treatment period. Re-escalation to 125/30 BID or re-titration in cases in which the subject has been off KarXT for a longer period of time (at least a week) is allowed and will require a discussion between the PI and the medical monitor. Additional changes to KarXT

dosing (e.g., temporary dose reductions) may be permitted as clinically indicated upon approval by the medical monitor.

Beginning after Visit 9/Day 84, interim visits will be completed with flexibility between in-clinic visits, approximately once every 4 weeks. Interim visits will be conducted by telemedicine; however, sites will have the option to schedule on-site interim visits as needed to facilitate subject retention and ensure adherence to study objectives. Additional unscheduled study visits may be conducted as needed.

All subjects will have questionnaires administered throughout the study (see Schedule of Assessments Table 2). Analyses of change from baseline in diagnostic measures will be performed.

Safety will be assessed through spontaneous AEs including AESIs, procholinergic and anticholinergic symptoms; SAEs and AEs leading to discontinuation of KarXT; SAS; BARS; AIMS; body weight; BMI; waist circumference; orthostatic vital signs; clinical laboratory assessments (hematology, clinical chemistry, coagulation, urinalysis, and drug screen), 12-lead ECG; physical examination; and C-SSRS will be evaluated throughout the study as scheduled. Section 11 provides complete details on these safety assessments.

Efficacy will be assessed through PANSS total score, PANSS-positive score, PANSS-negative score, PANSS Negative Marder Factor score, and CGI-S score at scheduled visits. Refer to Section 12 for more details.

Plasma concentrations of xanomeline and trospium will be evaluated. Details are provided in Section 13.

Exploratory assessments include cognition testing using CANTAB; prolactin levels; digital biomarkers of schizophrenia (US Only); Ecological Momentary Assessment (EMA) Patient Reported Outcomes (PRO; US Only) and EMA Verbal Learning and Memory Test (VLMT; US Only) which will be evaluated during scheduled visits or on specified study days. See Section 14 for more details.

A safety follow-up/end of study (EOS) visit (Visit 30/Day 371) will be performed for all subjects after the last dose of KarXT.

An Independent Safety Monitoring Committee (ISMC) will be responsible for periodically reviewing the safety data from this study and confirming that the study may continue.

Table 1 presents the Study Drug Dosing Scheme.

Table 1. Study Drug Dosing Scheme

Period:	Open-Label Extension Treatment[a]						EOT/ET	EOS/UNS
Day:	Day 1	Day 3 +1 day	Day 8[b] ±1 day	Day 14 ±2 days	Days 28 to 70 ±3 days	Days 84 to 350 ±3 days	Day 364 ±3 days	Day 371 ±3 days
Visit:	Visit 1	Visit 2	Visit 3 [b]	Visit 4	Visit 5	Visits 9 [c] to 28	Visit 29	Visit 30
Xanomeline/ trospium chloride (KarXT)*:	50/20 BID	100/20 BID	125/30 BID (Option: 100/20 BID)[d]	125/30 BID (Option: 100/20 BID)[d,e]	125/30 BID (Option: 100/20 BID)[d,e]	125/30 BID (Option: 100/20 BID)[d,e]	125/30 BID (Option: 100/20 BID) [d,e]	N/A
Comment(s):	2-day lead-in dose	Upward titration of dose	Upward titration of dose					7 (±3) days after the last dose or for ET from the study or UNS

Abbreviations: BID = twice daily; EOS = end of study; EOT = end of treatment; ET = early termination; N/A = not applicable; PI = principal investigator; UNS = unscheduled.

* All the KarXT doses are in mg xanomeline/mg trospium.

a. At Visit 1 (Day 1) subjects will initiate dosing with KarXT BID. Visits 2, 3, 4, 5, 6, 7, 8, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, and 30 are in-clinic/on-site visits. Visits 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28 are interim visits and should be conducted via telemedicine.
b. Subject to receive at least 8 doses of KarXT 100/20 prior to escalating to the KarXT 125/30 dose.
c. Beginning after Visit 9/Day 84, interim visits will be completed with flexibility between in-clinic visits, approximately once every 4 weeks.
d. All subjects who are increased to KarXT 125/30, depending on tolerability, will have the option to return to KarXT 100/20 BID.
e. Re-escalation to 125/30 BID or re-titration in cases where subject has been off KarXT for a longer period of time (at least a week) is allowed and will require a discussion between the PI and the medical monitor. Additional changes to KarXT dosing (e.g., temporary dose reductions) may be permitted as clinically indicated upon approval by the medical monitor.

7.2 Discussion of Study Design

The KarXT clinical development program includes this open-label extension study to evaluate the long-term safety, tolerability, and efficacy data for KarXT in subjects with schizophrenia who participated in either of the 2 Phase 3 double-blind clinical studies and completed the treatment period without any tolerability/safety issues.

This study will allow subjects that were randomized into a preceding Phase 3 study (KAR-007 or KAR-009) to reinstitute (or initiate treatment if a placebo subject) KarXT therapy. Subjects will receive KarXT (with the same lead-in dose of KarXT 50/20 BID), regardless of treatment assignment from the preceding Phase 3 study. Thus, subjects who received placebo during the preceding Phase 3 study who may not have demonstrated clinical benefit, nonetheless, may be considered appropriate for the current study, as all subjects will receive KarXT.

The dosing plan for this study has been established and follows the earlier studies. All eligible subjects will receive the same lead-in doses of KarXT (KarXT 50/20 BID). Dosing will be titrated to 100/20 BID on Day 3 and further titrated to 125/30 BID on Visit 3 (Day 8), unless the subject continues to experience AE(s) from the previous dose increase of KarXT.

During the study, all subjects who are increased to the highest dose of KarXT, depending on tolerability, will have the option to return to the next lower dose of KarXT (100/20 BID). Re-escalation to 125/30 BID or re-titration in cases where subject has been off KarXT for a longer period of time (at least a week) is allowed and will require a discussion between the PI and the medical monitor.

Beginning after Visit 9/Day 84, interim visits will be completed with flexibility between in-clinic visits, approximately once every 4 weeks. Interim visits will be conducted by telemedicine; however, sites will have the option to schedule on-site interim visits as needed to facilitate subject retention and ensure adherence to study objectives. Additional unscheduled study visits may be conducted as needed. A 52-week treatment phase is considered to be sufficient to demonstrate the long-term safety and tolerability of KarXT. A sample size of approximately 350 subjects is also determined to be an appropriate number of evaluable subjects to assess the long-term safety of KarXT administration. Section 5.2 details the nonclinical and clinical background information available on KarXT, including dose rationale.

7.3 End of Study

A subject will have fulfilled the requirements for study completion if/when the subject has completed the study treatment, including the EOS visit or the last scheduled visit as indicated in the Schedule of Assessments (Table 2) in accordance with the protocol.

7.4 Independent Safety Monitoring Committee

For the purpose of this study, the ISMC is an independent group of individuals with pertinent expertise that reviews on a regular basis accumulating safety and tolerability data from the

clinical study. The ISMC will include 3 clinicians and a reporting statistician. This committee will be responsible, on a periodic basis, for confirming the safety and tolerability of KarXT throughout the study, with particular focus on assessing for any new or long-term toxicities that might be involved with KarXT.

The reviews will allow a comparison of event rates and detection of safety signals, and to identify important safety information. The ISMC charter will contain the details of the types of data to be reviewed, the defined triggers for review, the minimum frequency of meetings (timed, if no triggers), and the communication plan for disseminating review recommendations.

8 SELECTION OF STUDY POPULATION

Section 7.1 provides information regarding the number of subjects planned to be enrolled.

8.1 Inclusion Criteria

Individuals must meet all of the following criteria to be included in the study:

1. Subject is aged 18 to 65 years, at time of enrollment into the preceding acute study (KAR-007 or KAR-009).
2. Subject is capable of providing informed consent.
    a. A signed informed consent form must be provided before any study assessments are performed.
    b. Subject must be fluent in (oral and written) English (United States only) or local language (Ukraine only) to consent.
3. Subject has completed the treatment period on study drug (through Day 35 -2 days) of Studies KAR-007 or KAR-009.
4. Subject resides in a stable living situation, in the opinion of the investigator.
5. Subject has an identified, reliable informant/caregiver willing to be able to address some questions related to certain study visits, if needed. An informant/caregiver may not be necessary if the subject has been the patient of the investigator for ≥1 year.
6. Women of childbearing potential (WOCBP) or men whose sexual partners are WOCBP must be willing and able to adhere to the contraception guidelines as defined in Section 8.4.1 and Appendix 1.

8.2 Exclusion Criteria

Subjects will be excluded from the study if 1 or more of the following criteria is/are applicable:

1. Risk for suicidal behavior during the study as determined by the investigator's clinical assessment and C-SSRS as confirmed by the following:
    a. Subject answers "Yes" to "suicidal ideation" Item 4 (active suicidal ideation with some intent to act, without specific plan) or Item 5 (active suicidal ideation with specific plan and intent) on the C-SSRS assessment.
    b. Nonsuicidal self-injurious behavior is not exclusionary.
2. Any clinically significant abnormality including any finding(s) from the physical examination, vital signs, ECG, or laboratory test at the end-of-treatment visit of studies KAR-007 or KAR-009 that the investigator, in consultation with the medical monitor, would consider to jeopardize the safety of the subject.
3. Female subject is pregnant, breast feeding or planning to become pregnant during the course of the study.

4. If, in the opinion of the investigator (and/or Sponsor), subject is unsuitable for enrollment in the study or subject has any finding that, in the view of the investigator (and/or Sponsor), may compromise the safety of the subject or affect his/her ability to adhere to the protocol visit schedule or fulfill visit requirements.
5. Subjects with extreme concerns relating to global pandemics such as coronavirus disease 2019 (COVID-19) that preclude study participation.
6. Risk of violent or destructive behavior.
7. Subjects participating in another investigational drug or device trial or planning on participating in another clinical trial during the course of the study.

8.3 Safety Laboratory Evaluations for Eligibility

Subjects may be enrolled into KAR-008 prior to receipt of the results from the safety laboratory evaluations collected on Visit 10 of the preceding acute study. These subjects will be dosed on Day 1 of KAR-008; however, subjects may be withdrawn from KAR-008 depending upon the clinical significance of the results of the Visit 10 safety laboratory evaluations at the discretion of the PI in consultation with the medical monitor. Abnormal lab values deemed clinically significant must be recorded as AEs. Subjects with elevated liver function tests (LFTs) per the DILI criteria must be withdrawn from further participation in KAR-008. Retesting of labs is allowed once, with the exception of elevated LFTs.

8.4 Study Withdrawal, Removal, and Replacement of Subjects

If a subject discontinues study treatment and is withdrawn from the study for any reason, the study site must immediately notify the medical monitor. The date and the reason for study discontinuation must be recorded on the electronic case report form (eCRF). Subjects who complete or discontinue early from the study will be asked to return to the study site within 7 (±3) days of the last administration of KarXT to complete EOS assessments as indicated in the Schedule of Assessments (Table 2).

In the event that a subject discontinues prematurely from the study because of a treatment emergent AE (TEAE) or serious TEAE, the TEAE or serious TEAE will be followed up until it resolves (returns to normal or baseline values) or stabilizes, or until it is judged by the investigator to no longer be clinically significant.

Once a subject is withdrawn from the study, the subject may not re-enter the study.

A subject may voluntarily withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following:

- progressive disease
- unacceptable toxicity or AE

- subject withdrawal of consent: at any time, a subject's participation in the study may be terminated at his/her request or on the basis of the investigator's clinical judgment; the reason for subject withdrawal will be noted on the eCRF
- intercurrent illness: a condition, injury, or disease unrelated to the primary diagnosis that became apparent during treatment and necessitated the subject's termination from the study
- general or specific changes in the subject's condition that renders them ineligible for further treatment according to the inclusion/exclusion criteria (eg, subject has need for a medication prohibited by the protocol)
- subject fails to adhere to the protocol requirements (eg, drug noncompliance [if a subject is off KarXT for >7 consecutive days])
- violation of entry criteria, ie, enrolled subjects who are later discovered not to meet eligibility criteria
- development of suicidal or assaultive behavior
- alcohol abuse or illegal drug use
- pregnancy, as indicated in Section 11.8
- Sponsor's decision to discontinue study

Subjects who withdraw from the study will be encouraged to complete the same final evaluations as subjects completing the study according to this protocol, particularly safety evaluations. The aim is to record data in the same way as for subjects who completed the study.

Reasonable efforts will be made to contact subjects who are lost to follow-up. A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study center. These efforts must be documented in the subject's file. Subjects with AEs ongoing at end of study will be followed until the AE is resolved or the subject is considered to be in stable condition.

The Sponsor has the right to terminate the study at any time in case of SAEs or if special circumstances concerning the KarXT become known, making further treatment of subjects impossible. In this event, the investigator(s) will be informed of the reason for study termination.

8.4.1 Pregnancy

No evidence of mutagenicity, or treatment effects on reproduction, fertility, or fetal parameters have been demonstrated in animals following administration of xanomeline, but there are no adequate and well-controlled studies in pregnant women (FDA Pregnancy Category B). Animal reproduction studies of trospium chloride have shown an adverse effect on the fetus, but potential benefits may warrant the use of the drug in pregnant women despite the risk (FDA Pregnancy Category C).

Therefore, WOCBP in this study must be willing to use a highly effective method of birth control (see Appendix 1 for a list of acceptable highly effective methods of contraception) during the study and for 30 days after the last dose of KarXT. WOCBP will have a urine pregnancy test on Day 0 (before receiving KarXT) and thereafter, as designated at other scheduled visits (Table 2). In case of positive urine pregnancy test result, a serum sample should be sent to the central laboratory to confirm the result. Pregnant women are excluded from this study because the effects of KarXT on the developing human fetus are unknown with the potential for teratogenic or abortifacient effects.

Because there is an unknown but potential risk for AEs in nursing infants secondary to treatment of the mother with KarXT, women who become pregnant must discontinue KarXT immediately.

The effects of KarXT on sperm are unknown. Male subjects whose sexual partners are WOCBP must agree to use a highly effective method of birth control (see Appendix 1 for a list of acceptable highly effective methods of contraception) and must not impregnate a sexual partner during or for 30 days after the last dose of KarXT. They must also agree to refrain from sperm donation for 30 days after the last dose of KarXT.

WOCBP will be instructed that known or suspected pregnancy occurring during the study should be confirmed and reported to the investigator. If a female subject becomes pregnant, the investigator must withdraw her from the study without delay. The subject must not receive any further doses of the KarXT. The investigator must notify the Sponsor or their designee of any female subject or female partner of a male subject that becomes pregnant while participating in the study. If the female subject or the female partner of the male subject is willing and able to consent to pregnancy follow-up, she will be followed until her pregnancy reaches term. Only those procedures that would not expose the pregnant female patient to undue risk will be performed. See Section 11.8 for further reporting and monitoring details.

Full details of the pregnancy will be recorded on the withdrawal page (exit form) of the eCRF, or a Pregnancy Reporting Form will be completed if the subject has completed the study. Notification of the pregnancy should be submitted via the Pregnancy Reporting Form within 24 hours of knowledge of the pregnancy. Pregnancy is not to be considered an AE; however, it must be reported using the same procedure as described for reporting SAEs, Section 11.7.4.

8.5 Completion of the Study or Lost to Follow-up

The study will be completed when all subjects have completed their study-related procedures in accordance with the protocol.

Every reasonable effort will be made to contact subjects who are lost to follow-up to obtain EOS information. Details regarding follow-up efforts are to be documented in the subject's medical records/source documentation.

8.6 Study Termination

The availability of any new adverse safety information related to KarXT may result in stopping the study. An investigator, Sponsor, or Institutional Ethics Committee (IEC)/Institutional Review Board (IRB) may take such actions. If the study is terminated for safety reasons, subjects will be notified immediately and assured that appropriate treatment and follow-up will be available. If an investigator terminates the study, the Sponsor, subjects, and IEC/IRB will be informed about the reason for such action. Similarly, if the Sponsor terminates the study, it will inform the investigators, the IEC/IRB, and the subjects of the reason for such an action. Similar notifications will be sent by the IEC/IRB if it takes such an action.

9 TREATMENTS

9.1 Details of Study Treatments

KarXT is formulated as hard hydroxypropyl methylcellulose oral capsules containing 2 distinct populations of drug beads, 1 of which is loaded with xanomeline tartrate and the other of which is loaded with trospium chloride. Each capsule contains the free base equivalent of xanomeline and trospium according to the desired dosage strength. In addition to the active ingredients, the drug beads contain microcrystalline cellulose (MCC). The beads are not coated and are formulated for immediate release of the active ingredients.

9.1.1 Identity of Study Treatments

Active study agents for treatment group will be size 0, Swedish orange, opaque, and hydroxypropyl methylcellulose hard capsules. For the 2-day lead-in period (Days 1 and 2), subjects will receive capsule strength KarXT 50/20 BID, followed by 2 capsules of KarXT 50/10 mg BID or a dosage of 100/20 mg BID for a total daily dose of 200/40 mg for the remainder of Week 1 (Days 3 to 7). At the beginning of Visit 3 (Day 8), dosing may be increased to 2 capsules of KarXT 62.5/15 mg or a dosage of 125/30 mg BID for a total daily dose of 250/60 mg, depending on tolerability. Investigators have the option to return a subject to KarXT 100/20 mg BID. Re-escalation to 125/30 BID or re-titration in cases where subject has been off KarXT for a longer period of time (at least a week) is allowed and will require a discussion between the PI and the medical monitor.

Additional changes to KarXT dosing (e.g., temporary dose reductions) may be permitted as clinically indicated upon approval by the medical monitor (see also Section 9.4).

KarXT 50/10 mg is composed of 44.4% xanomeline tartrate, 5.8% trospium chloride, excipients 37.59% MCC, 11.5% lactose monohydrate, 0.3% ascorbic acid and 0.5% talc in a size 0, Swedish orange, hydroxypropyl methylcellulose hard capsule.

KarXT 50/20 mg is composed of 33.4% xanomeline tartrate, 8.7% trospium chloride, excipients 39.8% MCC, 17.3% lactose monohydrate, 0.3% ascorbic acid and 0.5% talc in a size 0, Swedish orange, hydroxypropyl methylcellulose hard capsule.

KarXT 62.5/15 mg is composed of 41.7% xanomeline tartrate, 6.5% trospium chloride, excipients 38.1% MCC, 12.9% lactose monohydrate, 0.3% ascorbic acid and 0.5% talc in a size 0, Swedish orange, hydroxypropyl methylcellulose hard capsule.

All investigational agents are to be stored according to requirements as specified on the Investigational Product label.

9.1.2 Packaging and Labeling

The study packaging and labeling will be performed by Corealis Pharma, located in Laval, Quebec, Canada and Catalent Pharma Solutions, located in Winchester, Kentucky (labelling for

the US sites), and Catalent Pharma Solutions, located in Philadelphia, Pennsylvania (labelling for Ukrainian sites). All packaging and labeling operations will be performed according to Good Manufacturing Practice for Medicinal Products and the relevant regulatory requirements.

Bulk supply bottles are labeled with the name of the drug, recommended storage conditions, the name and address of the manufacturer and the Investigational Use Statement (for the US sites: "Caution: New Drug – Limited by Federal [USA] Law to Investigational Use" and for the Ukrainian sites: "For clinical trial use only" or similar wording).

Further details on labeling of investigational product will be provided in the Pharmacy Manual.

9.1.3 KarXT Storage

Prior to dispensing KarXT to the subjects, it must be stored at controlled room temperature 15˚C-25˚C.

9.1.4 KarXT Retention

KarXT must be retained until completion or termination of the study, and written authorization from the Sponsor has been received. All unused and used KarXT must be destroyed at the site or returned, as specified by Sponsor. It is the investigator's responsibility to ensure that the Sponsor has provided written authorization prior to return or destruction, and that appropriate records of the disposal are documented and maintained. No used or unused KarXT may be disposed until fully accounted for by the study monitor.

9.2 Dosage Schedule

Subjects who roll over into KAR-008 will start dosing with KarXT on Day 1 of the current study. Baseline/Day 0 procedures must be completed prior to Day 1 and preferably on the same day as Visit 10 (Day 35) of the preceding acute study KAR-007 or KAR-009. The assessments performed on Visit 10 (Day 35) of studies KAR-007 or KAR-009 will be considered as baseline assessments along with any additional procedures that must be performed up to Day 1 of the current study.

The first dose of the KarXT will be self-administered in the morning of Day 1 and the last dose will be self-administered in the morning of EOT Visit (Day 364). KarXT should be administered daily BID on an empty stomach (ie, at least 1 hour before a meal or 2 to 3 hours after a meal). Some considerations for dosing and PK blood withdrawals are provided in the subsections below. As described in Section 10.2, KarXT dosing adherence will be monitored using AiCure Technology.

9.2.1 Day 0

- The site pharmacist will prefill 1 child resistant pill bottle with sufficient quantities of 50mg/20mg of KarXT for the first 2 days of dosing.

- Sites will send the subject home with instruction to begin self-administration of KarXT BID in the morning of Day 1.
- For all KarXT doses, the first dose is to be self-administered in the morning and the evening dose will be self-administered at 12 (±4.5) hours after the morning dose.
- Remind the subject to bring their pill bottle to the next clinic visit.

9.2.2 Visit 1/Day 1 Dosing

- Initiate BID dosing with KarXT 50/20 x 4 doses.
- Subjects who remain on-site for Day 1 should self-administer KarXT using the AiCure device after completing AiCure training and registration.
- All subjects must have taken 4 doses of the KarXT 50/20 before dose escalation to KarXT 100/20 BID. Subjects should be instructed to contact the investigator in the event they did not take all 4 doses of KarXT 50/20 prior to Visit 2/Day 3.

9.2.3 Visit 2/Day 3 Dosing

- The site pharmacist will prefill 1 child-resistant bottle with a sufficient quantity of 50mg/10mg pills to accommodate BID dosing of KarXT at 100/20 level until the next clinic visit.
- Initiate BID dosing with KarXT 100/20 using the AiCure device. Subjects who have not taken their morning dose of 50/20 KarXT at the time of the study visit should receive their first dose of KarXT 100/20 at the time of the study visit. Subjects who have not yet completed AiCure training and registration must do so prior to dosing.
- All the subjects must have taken at least 8 doses of the KarXT 100/20 before dose escalation to KarXT 125/30 BID. Subjects should be instructed to contact the investigator in the event they did not take at least 8 doses of KarXT 100/20 prior to Visit 3/Day 8.
- Remind the subject to bring their pill bottle to the next clinic visit.

9.2.4 Visit 3/Day 8

- If dose escalation to the KarXT 125/30 level is confirmed by investigator order, the site pharmacist will prefill 1 child resistant bottle with a sufficient quantity of 62.5 mg/15 mg pills to accommodate BID dosing of KarXT at 125/30 level until the next clinic visit.
- If the subject has not yet taken their morning dose of 100/20 KarXT at the time of the study visit, the subject should receive their first dose of KarXT 125/30 at the time of the study visit.
- A single PK sample should be drawn at Visit 3/Day 8, and the dose of KarXT and time of most recent dosing should be recorded. Whenever possible, the PK sample should be obtained within 1 to 2 hours of dosing.

- Remind the subject to bring their pill bottle to the next clinic visit.

In the event that the subject is not escalated to KarXT 125/30, in accordance with investigator order, dispense sufficient quantities of 50 mg/10 mg pills to continue BID dosing of KarXT at the 100/20 level until next clinic visit.

9.2.5 Visit 4/Day 14 Dosing and PK Considerations

- If dose of KarXT 125/30 BID was confirmed by investigator order, the site pharmacist will prefill 1 child resistant bottle with a sufficient quantity of 62.5 mg/15mg pills to accommodate BID dosing of KarXT at 125/30 level until the next clinic visit.
- A single PK sample should be drawn at Visit 4/Day 14, and the dose of KarXT and time of most recent dosing should be recorded.
- Remind the subject to bring their pill bottle to the next clinic visit.

If dose of KarXT 100/20 BID was confirmed by investigator order, dispense sufficient quantities of 50 mg/10 mg pills to continue BID dosing of KarXT at the 100/20 level until next clinic visit.

9.2.6 Visits 5 to 8 (Days 28 to 70) Dosing

- If dose of KarXT 125/30 BID was confirmed by investigator order, the site pharmacist will prefill 1 child resistant bottle with a sufficient quantity of 62.5 mg/15 mg pills to accommodate BID dosing of KarXT at the 125/30 level until the next clinic visit.
- Remind the subject to bring their pill bottle to the next clinic visit.

If dose of KarXT 100/20 BID was confirmed by investigator order, dispense sufficient quantities of 50 mg/10 mg pills to continue BID dosing of KarXT at the 100/20 level until next clinic visit.

9.2.7 Visits 9 to 29 (Days 84 to 364) Dosing

- If dose of KarXT 125/30 BID was confirmed by investigator order, the site pharmacist will prefill two child resistant bottles with a sufficient quantity of 62.5 mg/15 mg pills to accommodate BID dosing of KarXT at the 125/30 level until the next clinic visit.
- For Days 84, 168, and 280, a single PK sample will be collected and the dose of KarXT and time of most recent dosing should be recorded.
- See Section 9.4.1 for management of KarXT dose changes and PK sampling.
- Remind the subject to bring their pill bottles to the next clinic visit.

If dose of KarXT 100/20 BID was confirmed by investigator order, dispense sufficient quantities of 50 mg/10 mg pills to continue BID dosing of KarXT at the 100/20 level until next clinic visit.

9.3 Measures to Minimize Bias: Study Treatment Assignment

9.3.1 Method of Study Treatment Assignment

The 9-digit Subject Number previously assigned to the subject in the study KAR-007/KAR-009 will continue to be used in the current study KAR-008. This number will be associated with the subject throughout the current study.

9.3.2 Blinding

This is an open-label study; therefore, blinding is not applicable.

9.4 Dosage Modification

Subjects will self-administer the KarXT as described in Section 7.1 and in accordance with the Schedule of Assessments (Table 2). The KarXT doses were selected based on the previous preclinical and clinical studies (see Section 5.2). Per the protocol, subjects will be evaluated for dose adjustments starting at Visit 3 through the remainder of the treatment period (see Section 9.2).

Additional changes to KarXT dosing (e.g., temporary dose reductions) may be permitted as clinically indicated upon approval by the medical monitor.

9.4.1 Extended Dosing Interruptions and Re-titration

Re-escalation to 125/30 BID or re-titration in cases where subject has been off the KarXT for a longer period of time (at least a week) is allowed and will require a discussion between the principal investigator (PI) and the medical monitor.

All subjects approved by the PI and medical monitor will resume KarXT by repeating the lead-in dosing scheme used at the start of study. Subjects will start with a lead-in dose of KarXT 50/20 BID for the first 2 days after restarting study drug. Then the dose will be titrated to 100/20 BID for at least the next 4 days, allowing the subject to adjust to KarXT before receiving a higher dose of 125/30 BID after restarting study drug, unless the subject is continuing to experience AEs from the previous dose, in which case the subject will remain on KarXT 100/20 BID.

9.5 Treatment Accountability and Compliance

The pharmacist or other designated individual will maintain records of study treatment delivered to the study site, the inventory at the study site, the distribution to each subject, and the return of materials to the Sponsor or designee for storage or disposal. These records should include dates, quantities, batch/serial numbers, expiration dates, temperature log, and unique code numbers assigned to the product and study subjects.

Administration of KarXT will be supervised by study site personnel (during in-clinic visits) and by a digital compliance tool to ensure adherence (AiCure technology). The pharmacist (or designee) will be responsible for dispensing KarXT into labeled child-resistant pill bottles for subjects use when at home. The quantity of KarXT capsules dispensed should be sufficient to cover the period (including visit window) until next planned study visit. Please refer to the Schedule of Assessments in Section 10 and the study Pharmacy Manual for details.

Investigators will maintain records that adequately document that the subjects were provided with the correct study treatment supply and reconcile the usage of the study drug. Investigational product will not be returned to the Sponsor or designee or destroyed until accountability has been fully monitored through the end of the study. KarXT accountability will be assessed periodically by the assigned study monitor.

9.6 Prior and Concomitant Therapy

9.6.1 Prior and Concomitant Medications

Concomitant medications ongoing as of Visit 10/Day 35 of the preceding acute study (KAR-007 or KAR-009) will be captured in the eCRF as baseline therapy. Thereafter, all medications and other treatments taken by the subject during the study, including those treatments initiated before the start of the study drug administration, must be recorded on the KAR-008 eCRF.

Restricted prior therapies are provided below.

During the study (ie, from the time of enrollment at baseline visit [Day 0] until study completion (EOS), subjects should refrain from the use of any new concomitant medications without the prior approval of the investigator. The administration of any other concomitant medications during the study period is prohibited without the prior approval of the investigator unless its use is deemed necessary in a medical emergency. Any medication or therapy that is taken by or administered to the subject during the course of the study must be recorded in the eCRF. The entry must include the dose, regimen, route, indication, and dates of use.

All the subjects enrolled into the study must not take the below mentioned prohibited medications for the duration of the treatment period.

- Oral or long acting injectable antipsychotic medications, monoamine oxidase inhibitors, mood stabilizers (ie, lithium), anticonvulsants (eg, lamotrigine, Depakote), tricyclic antidepressants (eg, imipramine, desipramine), selective serotonin reuptake inhibitors, or any other psychoactive medications except for anxiolytics that were taken on an as needed basis (eg, lorazepam, chloral hydrate).

Note: Please direct questions relating to prohibited medications to the medical monitor.

9.6.2 Concomitant Medications for Anxiety and/or Sleep Aid

Subjects are allowed to take benzodiazepines (up to 4 mg lorazepam/day or equivalent) for anxiety, agitation, and insomnia on a PRN basis. Subjects may also use non-benzodiazepine

medications (eg, zolpidem, zaleplon) as a sleep aid, also on a PRN basis. Study sites must record the use of such medications in the eCRF and subject's source document.

Note: Cognition testing should not be done within 8 hours of receiving a benzodiazepine or sleep medication.

10 STUDY PROCEDURES

Table 2 outlines the timing of procedures and assessments to be performed throughout the study. Section 11.6 specifies laboratory assessment samples to be obtained. See Sections 11, 12, 13, and 14 for additional details regarding efficacy, safety, PK, and exploratory assessments, respectively.

COVID-19 testing will be completed in accordance with clinical site standard operating procedures. If a subject tests positive for COVID-19 during the study, they may be quarantined as needed and any scheduled visits should be rescheduled or conducted via telemedicine per the discretion of the investigator. If the subject requires hospitalization, an SAE should be reported and the subject should be followed up as outlined in Section 11.7.3.

Table 2. Schedule of Assessments

DAY	0	1	3 (+1d)	8 (± 1d)	14 (± 2d)	28 (± 3d)	42 (± 3d)	56 (± 3d)	70 (± 3d)	84 (± 3d)	98 (± 3d)	112 (± 3d)	126 (± 3d)	140 (± 3d)	154 (± 3d)	168 (± 3d)
WEEK		**1**			**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**
VISIT	**Baseline[1]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10[a]**	**11**	**12**	**13**	**14**	**15**
TYPE OF VISIT	Clinic		Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic
PROCEDURE																
Written informed consent	X															
Subject eligibility verification	X															
Urine pregnancy test (WOCBP only)[b]	(X)[2]			X	X	X	X	X	X	X		X		X		X
Urine drugs of abuse and alcohol testing[c]	(X)[2]		X	X	X	X	X	X	X	X		X		X		X
Review of inclusion/exclusion criteria	X															
Height, body weight, BMI, waist circumference[d]	X				X	X	X	X	X	X		X		X		X
Complete physical examination[e]	X															
Targeted physical examination[f]	(X)[2]			X	X	X	X	X	X	X		X		X		X
Spontaneous AEs[g]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review of concomitant medications[h]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs: BP and HR[i]	X		X	X	X	X	X	X	X	X		X		X		X
Resting ECG (12-lead)[j]	X				X							X				
Blood samples for clinical laboratory tests[k]	X				X	X			X			X				X
Blood sample for prolactin[l]	X				X							X				
Functional constipation inquiry[m]	X		X	X	X	X	X	X	X	X		X		X		X
Determination of dose titration				X	X											
PK blood draw[n]				X	X					X						X
PANSS[o]	X				X	X		X		X		X		X		X
C-SSRS[p]	X		X	X	X	X	X	X	X	X		X		X		X
CGI-S scale	X				X	X		X		X		X		X		X
Cognition testing[q]	X					X		X		X						X

DAY	0	1	3 (+1d)	8 (± 1d)	14 (± 2d)	28 (± 3d)	42 (± 3d)	56 (± 3d)	70 (± 3d)	84 (± 3d)	98 (± 3d)	112 (± 3d)	126 (± 3d)	140 (± 3d)	154 (± 3d)	168 (± 3d)
WEEK		**1**			**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**
VISIT	**Baseline[l]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10[a]**	**11**	**12**	**13**	**14**	**15**
TYPE OF VISIT	Clinic		Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic
PROCEDURE																
SAS	X					X						X				
BARS	X					X						X				
AIMS	X					X						X				
AiCure registration and training[r]	X															
KarXT dispensed	X		X	X	X	X	X	X	X	X		X		X		X
Subject self-administration of KarXT using AiCure app[s]		X		X	X	X	X	X	X	X	X	X	X	X	X	X
EMA registration and training[t]			X													
EMA PRO[u]			X		X	X		X		X		X		X		X
EMA VLMT[v]						X		X		X		X		X		X
Digital biomarkers using AiCure app[w]			X	X	X	X		X		X		X		X		X

Table 2 Schedule of Assessments (Continued from Visits 16 to 30)

DAY	182 (± 3d)	196 (± 3d)	210 (± 3d)	224 (± 3d)	238 (± 3d)	252 (± 3d)	266 (± 3d)	280 (± 3d)	294 (± 3d)	308 (± 3d)	322 (± 3d)	336 (± 3d)	350 (± 3d)	364 (± 3d)	371 (± 3d)
WEEK	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52**	**53**
VISIT	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29 (EOT/ ET)**	**30 (EOS/ UNS)[3]**
TYPE OF VISIT	Interim	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic	Clinic
PROCEDURE															
Urine pregnancy test (WOCBP only)[b]		X		X		X		X		X		X		X	X
Urine drugs of abuse and alcohol testing[c]		X		X		X		X		X		X		X	X
Height, body weight, BMI, waist circumference[d]		X		X		X		X		X		X		X	X
Complete physical examination[e]															X
Targeted physical examination[f]		X		X		X		X		X		X		X	
Spontaneous AEs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review of concomitant medications[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs: BP and HR[i]		X		X		X		X		X		X		X	X
Resting ECG (12-lead)[j]		X						X						X	
Blood samples for clinical laboratory tests[k]				X				X				X		X	
Blood sample for prolactin[l]		X						X						X	
Functional constipation inquiry[m]		X		X		X		X		X		X		X	X
PK blood draw[n]								X						X[4]	
PANSS[o]		X		X		X		X		X		X		X	X
C-SSRS[p]		X		X		X		X		X		X		X	X
CGI-S scale		X		X		X		X		X		X		X	X
Cognition testing[q]						X						X		X[4]	
SAS		X						X						X	X

DAY	182 (± 3d)	196 (± 3d)	210 (± 3d)	224 (± 3d)	238 (± 3d)	252 (± 3d)	266 (± 3d)	280 (± 3d)	294 (± 3d)	308 (± 3d)	322 (± 3d)	336 (± 3d)	350 (± 3d)	364 (± 3d)	371 (± 3d)
WEEK	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52**	**53**
VISIT	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29 (EOT/ ET)**	**30 (EOS/ UNS)[3]**
TYPE OF VISIT	Interim	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic	Clinic
PROCEDURE															
BARS		X						X						X	X
AIMS		X						X						X	X
KarXT dispensed		X		X		X		X		X		X			
Subject self-administration of KarXT using AiCure app[s]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
EMA PRO[u]		X		X		X		X		X		X			
EMA VLMT[v]		X		X		X		X		X		X			
Digital biomarkers using AiCure app[w]		X		X		X		X		X		X			

Abbreviations: AE = adverse event; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; BL = baseline; BMI = body mass index; BP = blood pressure; CGI-S = Clinical Global Impression–Severity scale; C-SSRS = Columbia-Suicide Severity Rating Scale; d = day; ECG = electrocardiogram; EMAW = EMA Wellness; EOS = end of study; EOT = end of treatment; ET = early termination; HR = heart rate; PANSS = Positive and Negative Syndrome Scale; PK = pharmacokinetic; QTcF = QT interval corrected by Fridericia; SAS = Simpson-Angus Rating Scale; UNS = unscheduled visit.

1. Baseline Day 0 assessments should be rolled over from Day 35/Visit 10 of the preceding study (KAR-007 or KAR-009) whenever possible (exception: cognition which should be rolled over from Day 32). Includes pregnancy testing, complete physical exam, vital signs, ECG, safety laboratory evaluations, functional constipation inquiry, PANSS, C-SSRS, CGI-S, SAS, AIMS and BARS.
2. (X) = Optional and to be completed only if Day 0 visit does not take place on the same day of Day 35/Visit 10 of the preceding study. See footnotes for additional details.
3. Other assessments as needed.
4. This procedure is optional and should only be performed for participants who have terminated early.

a. Beginning after Visit 9/Day 84, interim visits will be completed every 4 weeks with flexibility between the in-clinic visits, which will occur every month. Interim visits will be conducted by site staff using telemedicine (audio only, or audio + video). When needed, the sites will have the option to schedule a subject for an in-clinic visit.

b. A urine pregnancy test for WOCBP should be performed at scheduled visits. If a urine pregnancy test is positive, a serum sample should be sent to central laboratory for confirmation of the result. A new urine pregnancy test should be performed on Day 0 visit only if subject left the inpatient unit after completion of Visit 10 of the preceding acute study but prior to completion of the Day 0 procedures of the current study.
c. A National Institute on Drug Abuse-5 (NIDA-5) urine drug screen (cannabinoids or marijuana, phencyclidine, amphetamines, opiates, and cocaine) and test for alcohol (breathalyzer or urine alcohol level) will be performed at the indicated scheduled visits. Should be performed on Day 0 visit only if subject left the inpatient unit after completion of Visit 10 of the preceding acute study but prior to completion of the Day 0 procedures of the current study.
d. Baseline height is recorded from Study KAR-007/KAR-009 Screen visit. Baseline body weight, BMI and waist circumference recorded from KAR--007/-009 Visit 10. At the indicated study visits, body weight and waist circumference will be measured and BMI calculated.
e. A complete physical examination includes body temperature (°C), general appearance, head/eyes/ears/nose/throat (HEENT), examination of thorax and, assessment of cardiac, musculoskeletal, and circulatory systems, palpations for lymphadenopathy, and limited neurological examination.
f. A targeted physical examination includes at a minimum body temperature, a check of general appearance, as well as examination of organ systems that are relevant to the investigator based on review of the subject's reported AEs, review of systems, or concomitant medication use. These also include symptom-driven physical examinations which will be performed as clinically indicated at any study visit. A targeted physical examination at Day 0 is optional, and only required if the subject has reported a new AE in the time since completing Visit 10 of the preceding acute study.
g. Adverse events as reported by subjects or observed by clinical staff. Adverse events ongoing as of Visit 10 of the preceding acute study will be recorded in the KAR-008 Medical History eCRF. Adverse events occurring after dosing with KarXT in the current study will be recorded in the KAR-008 AE eCRF. One PK blood sample may be drawn if a relevant/significant AE (based on medical judgment) is reported during a scheduled visit or if there is a dose titration or a relevant/significant AE reported during an unscheduled visit (no multiple draws). For interim visits, spontaneous AEs will be collected by telemedicine.
h. Concomitant medications ongoing as of Visit 10/Day 35 of the preceding acute study will be captured in the eCRF as baseline therapy. Thereafter, all medications and other treatments taken by the subject during the study, including those treatments initiated before the start of the study, must be recorded on the KAR-008 eCRF. For interim visits, concomitant medications will be collected by telemedicine.
i. Vital signs measurements should be taken at all in-clinic visits, while the subject is supine and standing after 2 minutes. BP includes systolic and diastolic BP and is to be taken in the same arm for the duration of the study. During in-clinic visits orthostatic vital signs should occur 2 (±1) hours after morning dose of KarXT whenever possible.
j. ECG should be obtained within 1 to 2 hours post morning dose whenever possible. ECG at all indicated visits should be performed before blood withdrawal for any safety laboratory tests and/or PK analysis. ECGs will be transmitted electronically to a central reader for determination of ventricular rate (bpm), PR (msec), QRS (msec), QT (msec), and QTcF (msec) measurements.
k. Refer to Section 11.6 for individual laboratory tests. For urinalysis, a urine dipstick will be performed at the site. In the event of abnormalities, the sample will be sent to the central laboratory for full microscopic urinalysis.
l. Prolactin sample is optional when using local labs.
m. Functional constipation inquiry: At specified visits, subjects will be asked whether they have experienced constipation (per the ROME III criteria and Bristol Stool Form Scale; see Appendix 2) since the last visit and if yes, whether the constipation required intervention. If the subject answers yes, sites are instructed to ask subjects to provide event date and ensure the event is documented as an AE and treatment is documented as concomitant medication.
n. PK blood samples will be collected on Days 8, 14, 84, 168, and 280. At Day 8 the PK sample should be obtained within 1 to 2 hours post dose whenever possible. In cases of dose reduction, re-escalation, or re-titration, an additional PK sample may be collected per investigator discretion in consultation with the medical monitor.
o. It is recommended, if at all possible, that the PANSS assessment should be performed before all the other scale assessments for all visits at which it is performed.

p. The "since last visit" version should be used for C-SSRS administration. At the Unscheduled visit, the C-SSRS should be performed to monitor subjects for suicidality.
q. Cognition testing is performed using CANTAB. Cognition testing should not be done within 8 hours of receiving a benzodiazepine or sleep medication.
r. Refer to the Study Operations Manual for details. AiCure should be used to self-administer KarXT beginning on Day 1 whenever possible. All subjects must begin using AiCure adherence monitoring to self-administer KarXT no later than Visit 2, Day 3.
s. Subjects must complete AiCure training and registration no later than Visit 2/Day 3 and prior to escalating to the 100/20 KarXT dose. See Study Operations Manual for more details.
t. US Only. See Study Operations Manual for additional details.
u. EMA PRO (US Only) will be completed by the subject at home on a cellular device 3 times per day for 7 days every 28 days, beginning on Day 29. An abbreviated version of the assessment will be utilized on Days 4-6 and 15-17 to familiarize subjects with the process. Refer to Study Operational Manual for details.
v. Cognitive insight (US Only) will be assessed using the EMA VLMT. The assessment will be completed by the subject at home on a cellular device 1 time per day for 2 days every 28 days beginning on Day 32. Refer to Study Operational Manual for details.
w. Digital biomarkers of schizophrenia (US Only) will be calculated through completion of a smartphone-based assessment daily by the subject for 3 days collected initially on Days 4-6, 9-11, and 15-17. Subsequently subjects will complete assessments daily for 3 days every 28 days, beginning on Day 29. Refer to Study Operational Manual for details.

10.1 Informed Consent

Informed consent forms must be approved for use by the reviewing Independent Ethics Committee (IEC)/Institutional Review Board (IRB). Before performing any study-related procedures, the investigator (or designee) will obtain written informed consent from the subject and/or caregiver (Ukraine only).

10.2 Study Procedures

Assessments and their timing are to be performed as outlined in the Schedule of Assessments (Table 2). Section 11.6 specifies laboratory assessment samples to be obtained.

Safety assessments are described in Section 11 and include spontaneous AEs including AESIs; procholinergic and anticholinergic symptoms, SAEs and AEs leading to discontinuation of the KarXT; SAS; BARS; AIMS; body weight; BMI; waist circumference; orthostatic vital signs; ECG; clinical laboratory assessments (hematology, clinical chemistry, coagulation, urinalysis, and drug screen); physical examination; and C-SSRS.

Efficacy assessments are described in Section 12 and include PANSS and CGI-S scores.

PK assessments are described in Section 13.

Exploratory assessments are described in Section 14 and include cognition testing using CANTAB; prolactin levels; digital biomarkers of schizophrenia; EMA PRO; and EMA VLMT.

The investigator may, at his/her discretion, arrange for a subject to have an unscheduled assessment, especially in the case of AEs that require follow-up or are considered by the investigator to be possibly related to the use of KarXT. The unscheduled visit page in the eCRF must be completed. The assessments and procedures that may be performed during an unscheduled visit are outlined in the Schedule of Assessments (Table 2). Additional assessments can be performed as needed, at the discretion of the investigator, and following discussion with the medical monitor.

Study discontinuation procedures are described in Section 8.4 and Section 8.6.

10.2.1 AiCure Adherence Technology

AiCure technology will be used to monitor study medication adherence in all subjects, both in the US and the Ukraine. Subjects must complete registration and training and begin utilizing AiCure technology no later than Visit 2/Day 3, prior to escalating from 50/20 to 100/20 KarXT. See Operations Manual for additional details. Additionally, the AiCure technology will be used to capture Digital Biomarker Assessment of schizophrenia symptoms of subjects in the US only.

Medication Adherence (US and Ukraine):

This study will employ a medication adherence monitoring platform (herein after referred to as Platform) for all subjects in the study. The Platform uses artificial intelligence on smartphones to

confirm medication ingestion. In addition, built-in reminders and a communication system allow real-time intervention in case of drug interruptions.

Use of this Platform will in no way supersede or replace the physician and/or prescribed medication protocol of the subjects. Because the Platform does not change the medication protocol of the subjects, but rather encourages adherence to the predefined protocol, use of this Platform presents minimal risk to the subjects. Use of the Platform will be required for all subjects in the study.

The monitoring Platform requires that all subjects take each dose of the medication while using a smartphone. Participants will download the AiCure application on their personal smartphone device; for participants who do not have a smartphone or do not wish to use their personal smartphone, site personnel will provide the participant with one of the preloaded backup provisioned devices.

When at home, study subjects will receive a medication reminder at a time within a predefined window. This notification reminds subjects to take their medication dose while using the Platform. Subjects will follow a series of prescribed steps in front of the front-facing webcam to visually confirm their ingestion of the medication. The application on the smartphone will make an automated determination of whether the subject has properly taken their medication at the prescribed time. There is no need for a healthcare provider to review the administration, nor would a healthcare provider need to be available at the time the subject takes their medication. The amount of guidance that the device provides to the subject is automatically reduced as the subject becomes more proficient at using the application.

Digital Biomarker Assessment (US only):

For subjects enrolled at US sites only, subjects will be performing brief smartphone-based assessments using the AiCure application. Video and audio of participant behavior captured during these assessments will be used to calculate visual and auditory markers of schizophrenia symptomatology. These digital biomarkers will be used as exploratory efficacy endpoints to measure change from baseline in disease severity. See Section 14.4 for endpoint discussion. The material will be presented to subjects in one of two ways. In the first, material will be presented to subjects, and will include questionnaires provided at regular intervals during the study. Images may also be shown to subjects, and they will be asked to describe each image in a few sentences to the camera of the smartphone.

Data Collected on the AiCure Platform:

After the device confirms proper medication ingestion, video recordings will be encrypted and transmitted to a secure centralized location for further analysis, including testing for duplicate enrollment. Video and audio recordings from the Digital Biomarker assessments will be encrypted and transmitted in a similar manner. The captured data and video is reviewable through a roles and rules restricted system ensuring privacy of the information. The system is compliant with applicable US and European data privacy laws, including General Data

Protection Regulation (GDPR) (EU) 2016/679 the Health Insurance Portability and Accountability Act (HIPAA), which protects the privacy and security of healthcare information.

Phone numbers of the patients may also be collected and stored in an encrypted manner. Storing the phone numbers will allow for direct communication with patients, including automated messaging from the Platform device and contact by healthcare providers or other monitoring personnel. At no time is the phone number visible to healthcare providers or monitoring personnel. Individuals outside the clinical sites will not be provided with patient names, nor will they be given access to patient medical records.

The Platform may provide significant benefits to study subjects as well as to the other stakeholders in the trial. Subjects will benefit from rapid and tailored intervention in case of non-adherence (drug interruptions) without having to visit the clinic for unscheduled visits. Healthcare providers will have access to real-time and continuous adherence data without having to rely on self-reported data or frequent study visits by patients. Subjects who regularly fail to take their medication will be contacted by healthcare providers or other study monitoring personnel for retraining.

11 SAFETY ASSESSMENTS

Safety assessments (spontaneous AEs including AESIs; procholinergic and anticholinergic symptoms; SAEs and AEs leading to discontinuation of the KarXT; SAS; BARS; AIMS; body weight; BMI; waist circumference; orthostatic vital signs; ECG; clinical laboratory assessments [hematology, clinical chemistry, coagulation, urinalysis, and drug screen]; physical examination; and C-SSRS) will be performed at protocol-specified visits, as specified in the Schedule of Assessments (Table 2).

11.1 Demographics, Medical History, and Psychiatric History

Demographic data, and medical and psychiatric history will be recorded from the Phase 3, double-blind, acute study (KAR-007/KAR-009).

Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs on the eCRF in accordance with Section 11.7. All changes that are not present at baseline or described in the past medical history and identified as clinically noteworthy must be recorded as AEs.

11.2 Vital Signs

Orthostatic vital signs (systolic and diastolic BP and heart rate measurements) will be evaluated at all scheduled visits indicated in the Schedule of Assessments (Table 2). All vital signs will be measured supine and standing after 2 minutes. Blood pressure measurements are to be taken in the same arm for the duration of the study. During in-clinic visits, beginning with Visit 2 (Day 3), orthostatic vital signs should occur 2 (±1) hours after morning dosing, whenever possible.

Vital sign measurements will be repeated if clinically significant or machine/equipment errors occur. Out-of-range BP, or heart rate measurements will be repeated at the investigator's discretion. Any confirmed, clinically significant vital sign measurements must be recorded as AEs.

11.3 Complete/Targeted Physical Examination

A complete physical examination (body temperature, general appearance, head/eyes/ears/nose/throat [HEENT], examination of thorax and abdomen, assessment of cardiac, musculoskeletal, and circulatory systems, palpations for lymphadenopathy, and limited neurological examination) will be performed at visits as specified in Table 2. Physical examinations will be performed by a physician or qualified designee.

A targeted physical examination includes at a minimum body temperature, a check of general appearance, as well as examination of organ systems that are relevant to the investigator, based on review of the subject's reported AEs, review of systems, or concomitant medication use. These also include symptom-driven physical examinations which will be performed as clinically indicated at any study visit.

11.4 Weight, Height, Body Mass Index, and Waist Circumference

The baseline height measurement will be recorded from the lead-in Study KAR-007 or KAR-009 Screen visit. The baseline body weight, BMI and waist circumference measurements will be recorded from the KAR-007 or KAR-009 Visit 10. At the indicated visits of the current study (Table 2), body weight and waist circumference will be measured and BMI calculated. All findings should be recorded in the eCRF.

11.5 Electrocardiograms

A 12-lead, resting ECG should be obtained within 1 to 2 hours post morning dose at the visits indicated in the Schedule of Assessments (Table 2), whenever possible. ECG at all scheduled visits should be performed before blood withdrawal for any safety laboratory tests and/or PK analysis.

ECGs will be transmitted electronically to a central reader for determination of ventricular rate (bpm), PR (msec), QRS (msec), QT (msec), and QTcF (msec) measurements. An assessment of normal or abnormal will be recorded; if the ECG is considered abnormal, the abnormality will be documented on the eCRF. ECGs will be repeated if clinically significant abnormalities are observed or artifacts are present.

11.6 Laboratory Assessments

Laboratory assessment samples (Table 3) are to be obtained at designated visits as detailed in the Schedule of Assessments (Table 2).

Table 3. Laboratory Assessments

Hematology	**Serum Chemistry**	**Urine Analysis (Dipstick)**
Full and differential blood count Hct Hb MCH MCHC MCV Platelet count RBC count WBC count with differential	ALT ALP AST Albumin Uric acid BUN or urea Carbon dioxide Creatinine Creatine kinase and subtypes Electrolytes (sodium, potassium, chloride, calcium, phosphorus) GGT Glucose LDH Total bilirubin Direct bilirubin Total cholesterol HDL LDL Triglycerides Total protein	Appearance pH Protein Glucose Ketone bodies Indicators of blood and WBCs Specific gravity Urobilinogen Occult blood WBCs
HbA1c (glycated Hb test)	**Prolactin**	
Coagulation		
PT Activated PTT Fibrinogen		
Pregnancy test: A urine pregnancy test for WOCBP should be performed per the schedule of assessments (Table 2). In case of positive urine pregnancy test result, a serum sample should be sent to the central laboratory to confirm the result.		
Full and microscopic urinalysis: Chemical exam: SG, pH, bilirubin, urobilinogen, protein, glucose, ketone, hemoglobin, leukocyte esterase, nitrite, ascorbic acid Microscopic exam: RBCs, WBCs, epithelial cells, bacteria, yeasts, parasites, casts, crystals		

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; GGT = gamma-glutamyl transpeptidase; HCG = human chorionic gonadotropin; Hb = hemoglobin; Hct = hematocrit; HDL = high density lipoprotein; LDH = lactate dehydrogenase; LDL = low density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; WBC = white blood cell; WOCBP = women of childbearing potential.

Venous blood of approximately 12 to 20 mL will be withdrawn for the tests listed above at scheduled time points as per Table 2.

A minimum volume of 10 mL will be obtained to perform urinalysis (if abnormalities observed on dipstick) and urine drug screen at scheduled time points as per Table 2.

Blood and urine samples (microscopic analysis) will be analyzed at a central laboratory facility. Urine samples will first be analyzed by dipstick at the site. If the results of the dipstick indicate abnormalities to be further investigated, the sample will be sent to the central laboratory and a microscopic analysis will be performed. All laboratory reports must be reviewed, signed, and dated by the investigator. A legible copy of all reports must be filed with both the subject's eCRF and medical record (source document) for that visit. Any laboratory test result considered by the investigator to be clinically significant should be considered an AE (clinically significant AEs include those that require an intervention). Clinically significant abnormal values occurring during the study will be followed up until repeat test results return to normal, stabilize, or are no longer clinically significant.

All the study subjects will be closely monitored for the drug-induced liver toxicity (detailed in Section 11.7.5), during the study.

Other Laboratory Assessments:

- A National Institute on Drug Abuse-5 (NIDA-5) urine drug screen (cannabinoids or marijuana, phencyclidine, amphetamines, opiates, and cocaine) will be performed using a dipstick throughout the study.
- Alcohol testing will be performed using a breathalyzer or urine alcohol test.

11.7 Adverse Events

11.7.1 Adverse Events

An AE is any symptom, physical sign, syndrome, or disease that either emerges during the study or, if present at screening/baseline, worsens during the study, regardless of the suspected cause of the event. All medical and psychiatric conditions (except those related to the indication under study) present at screening/baseline will be documented in the medical history eCRF. Changes in these conditions and new symptoms, physical signs, syndromes, or diseases should be noted on the AE eCRF during the rest of the study. Clinically significant laboratory abnormalities should also be recorded as AEs. Surgical procedures that were planned before the subject enrolled in the study are not considered AEs if the conditions were known before study inclusion; the medical condition should be reported in the subject's medical history.

In accordance with the protocol, the investigator and/or study staff will elicit AEs and intercurrent illness during and at the end of the study period and these will be recorded on the appropriate page of the eCRF. Adverse events will be elicited by asking the subject a nonleading question, for example, "Have you experienced any new or changed symptoms since we last asked?" The eCRF will be completed at the end of the study as soon as the results of the final lab tests are available.

Each AE is to be documented on the eCRF with reference to date of onset, duration, frequency, severity, relationship to KarXT, action taken with KarXT, treatment of event, and outcome. Furthermore, each AE is to be classified as being serious or nonserious. Changes in AEs and resolution dates are to be documented on the eCRF.

For the purposes of this study, the period of observation for collection of AEs extends from the time immediately after the administration of KarXT on Day 1 until the EOS or ET. Follow-up of the AE, even after the date of therapy discontinuation, is required if the AE persists until the event resolves or stabilizes at a level acceptable to the investigator.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the event should be noted. If the intensity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

The severity of AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 5.0 (Grades 1 through 5).

Specific guidelines for classifying AEs by intensity and relationship to KarXT are given in Table 4 and Table 5.

Table 4. Classification of Adverse Events by Intensity

MILD: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
MODERATE: An event that is sufficiently discomforting to interfere with normal everyday activities.
SEVERE: An event that prevents normal everyday activities.

Table 5. Classification of Adverse Events by Relationship to KarXT

UNRELATED: This category applies to those AEs that are clearly and incontrovertibly due to extraneous causes (disease, environment, etc).
UNLIKELY: This category applies to those AEs that are judged to be unrelated to the test drug but for which no extraneous cause may be found. An AE may be considered unlikely to be related to KarXT if or when it meets 2 of the following criteria: (1) it does not follow a reasonable temporal sequence from administration of the test drug; (2) it could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it does not follow a known pattern of response to the test drug; or (4) it does not reappear or worsen when the drug is readministered.
POSSIBLY: This category applies to those AEs for which a connection with the test drug administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related if or when it meets 2 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; or (3) it follows a known pattern of response to the test drug.
PROBABLY: This category applies to those AEs that the investigator feels with a high degree of certainty are related to the test drug. An AE may be considered probably related if or when it meets 3 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose (note that there are exceptions when an AE does not disappear upon discontinuation of the

drug, yet drug-relatedness clearly exists; for example, as in bone marrow depression, fixed drug eruptions, or tardive dyskinesia); or (4) it follows a known pattern of response to the test drug.

DEFINITELY: This category applies to those AEs that the investigator feels are incontrovertibly related to test drug. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose and recurs with re-exposure to drug (if rechallenge occurs); and (4) it follows a known pattern of response to the test drug.

Abbreviation: AE = adverse event.

11.7.2 Adverse Events of Special Interest

The AEs of special interest will be monitored and include orthostasis and liver function test elevations inclusive of drug-induced liver injury (DILI).

11.7.3 Serious Adverse Events

An SAE is any untoward medical occurrence, in the view of either the investigator or Sponsor, that:

- results in death,
- is life-threatening,
- results in inpatient hospitalization or prolongation of existing hospitalization (however, hospitalization for elective treatment of a pre-existing non-worsening condition is not considered an SAE; the details of such hospitalizations must be recorded on the medical history or physical examination page of the eCRF),
- results in persistent or significant disability/incapacity, and/or
- is a congenital anomaly/birth defect.

Other important medical events that may not be immediately life-threatening or result in death or hospitalization, based upon appropriate medical judgment, are considered SAEs if they are thought to jeopardize the subject and/or require medical or surgical intervention to prevent 1 of the outcomes defining an SAE. Serious AEs are critically important for the identification of significant safety problems; therefore, it is important to take into account both the investigator's and the Sponsor's assessment. If either the Sponsor or the investigator believes that an event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting.

11.7.4 Serious Adverse Event Reporting

An SAE occurring from the time the first dose of KarXT is administered, during the study, or within 1 week of stopping the treatment must be reported to the Catalyst Clinical Research Pharmacovigilance group and will be communicated to the Sponsor. Any such SAE due to any

cause, whether or not related to the KarXT, must be reported within **24 hours of occurrence or when the investigator becomes aware of the event**. Notification can be made using email.

Catalyst Clinical Research Pharmacovigilance email address: [redacted]

The event must be recorded on the standard AE eCRF. Preliminary reports of SAEs must be followed up by detailed descriptions later on, including clear and anonymized photocopies of hospital case reports, consultant reports, autopsy reports, and other documents when requested and applicable. SAE reports must be made whether or not the investigator considers the event to be related to the investigational drug.

Appropriate remedial measures should be taken to treat the SAE, and the response should be recorded. Clinical, laboratory, and diagnostic measures should be employed as needed in order to determine the etiology of the problem. The investigator must report all additional follow-up evaluations to the Catalyst Clinical Research Pharmacovigilance group within 24 hours of becoming aware of the additional information or as soon as is practicable. All SAEs will be followed up until the investigator and Sponsor agree the event is satisfactorily resolved.

Any SAE that is not resolved by the end of the study or upon discontinuation of the subject's participation in the study is to be followed up until it either resolves, stabilizes, returns to baseline values (if a baseline value is available), or is shown to not be attributable to the KarXT or procedures.

11.7.5 Drug-Induced Liver Injury

The sponsor has incorporated the following for monitoring of drug-induced liver injuries:

- *An increase of serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) to >3 × ULN should be followed by repeat testing within 48 to 72 hours of all 4 of the usual serum measures (ALT, AST, ALP, and total bilirubin) to confirm the abnormalities and to determine if they are increasing or decreasing. An inquiry should be made about the symptoms (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, and rash).*
- *Close observation should be initiated with ALT or AST >3 × ULN:*
    - *Repeat liver enzyme and serum bilirubin tests 2 or 3 times weekly. The frequency of retesting can decrease to once per week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic.*
    - *Obtain a more detailed history of symptoms and prior or concurrent diseases.*
    - *Obtain a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.*

- *Rule out acute viral hepatitis types A, B, C, D, and E, autoimmune or alcoholic hepatitis, non-alcoholic steatohepatitis, hypoxic/ischemic hepatopathy, and biliary tract disease.*
- *Obtain a history of exposure to environmental chemical agents.*
- *Obtain additional tests to evaluate liver function, as appropriate (eg, international normalized ratio, and/or direct bilirubin).*
- *Consider gastroenterology or hepatology consultations.*

- *Discontinuation of treatment should be considered if:*
  - *ALT or AST >8 × ULN*
  - *ALT or AST >5 × ULN for more than 2 weeks*
  - *ALT or AST >3 × ULN and (total bilirubin >2 × ULN or international normalized ratio >1.5)*
  - *ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (>5%)*
- *Hepatic adjudication of cases should include an evaluation for alternative causes such as viral, autoimmune, alcohol, hepatobiliary disorders, non-alcoholic steatohepatitis, concomitant medications, etc.*
- *Follow-up to resolution of elevated liver enzymes.*
- *Gamma-glutamyl transferase elevations alone should not prompt drug discontinuation.*

Subjects must be monitored closely. If close monitoring is not possible, the study drug should be discontinued.

11.7.5.1 Trial Discontinuation Criteria Other than DILI and Pregnancy

11.7.5.2 Individual Stopping Criteria

Based on NCI CTCAE v5.0, study drug will be discontinued in any subject who has a ≥ Grade 4 AE. Discontinuation or reduction in the dosage of the study drug for Grade 3 AEs other than DILI AEs (see Section 11.7.5) will be at the discretion of the investigator.

11.7.5.3 Trial Stopping Rules

The safety and tolerability aspects of KarXT will be overseen by an ISMC. The ISMC will meet periodically and review the unblinded data and will be responsible for advising the sponsor on ways to safeguard the interests of the clinical study subjects. The committee is expected to recommend sponsor whether to:

a. Continue the clinical study without modification; or
b. Continue the clinical study with modification (listing the specific modifications recommended); or

c. Terminate the study.

11.7.6 Suspected Unexpected Serious Adverse Reactions

Adverse events that meet all of the following criteria will be classified as suspected unexpected serious adverse reactions (SUSARs) and reported to the appropriate regulatory authorities in accordance with applicable regulatory requirements for expedited reporting:

- serious
- unexpected (ie, the event is not consistent with the safety information in the IB or package insert of generic trospium)
- there is at least a reasonable possibility that there is a causal relationship between the event and the study treatment

The investigator will assess whether an event is causally related to study treatment. The Sponsor (or Syneos Health) will consider the investigator's assessment and determine whether the event meets the criteria for being reportable as a 7-day or 15-day safety report. SUSARs that are fatal or life-threatening must be reported to the regulatory authorities and the IEC/IRBs (where required) within 7 days after the Sponsor (or Syneos Health) has first knowledge of them, with a follow-up report submitted within a further 8 calendar days. Other SUSARs must be reported to the relevant regulatory authorities and the IEC/IRBs within 15 calendar days after the Sponsor (or Syneos Health) first has knowledge of them.

The Sponsor (or Syneos Health) is responsible for reporting SUSARs and any other events required to be reported in an expedited manner to the regulatory authorities and for informing investigators of reportable events, in compliance with applicable regulatory requirements within specific timeframes. Investigators will notify the relevant IEC/IRBs of reportable events within the applicable timeframes.

11.7.7 Warnings and Precautions

Risk of Urinary Retention:

Trospium chloride tablets should be administered with caution to subjects with clinically significant bladder outflow obstruction because of the risk of urinary retention.

Angioedema:

Angioedema of the face, lips, tongue, and/or larynx has been reported with trospium chloride, the active ingredient in trospium chloride tablets. In one case, angioedema occurred after the first dose of trospium chloride. Angioedema associated with upper airway swelling may be life-threatening. If involvement of the tongue, hypopharynx, or larynx occurs, trospium chloride should be promptly discontinued and appropriate therapy and/or measures necessary to ensure a patent airway should be promptly provided.

Decreased Gastrointestinal Motility:

Trospium should be administered with caution to subjects with GI obstructive disorders because of the risk of gastric retention. Trospium chloride, like other antimuscarinic agents, may decrease GI motility and should be used with caution in subjects with conditions such as ulcerative colitis, intestinal atony, and myasthenia gravis.

Controlled Narrow-angle Glaucoma:

In subjects being treated for narrow-angle glaucoma, trospium chloride should only be used if the potential benefits outweigh the risks and in that circumstance only, with careful monitoring.

Central Nervous System Effects:

Trospium chloride is associated with anticholinergic CNS effects. A variety of CNS anticholinergic effects have been reported, including dizziness, confusion, hallucinations, and somnolence. Subjects should be monitored for signs of anticholinergic CNS effects, particularly after beginning treatment or increasing the dose. Advise subjects not to drive or operate heavy machinery until they know how trospium chloride affects them. If a subject experiences anticholinergic CNS effects, dose reduction or drug discontinuation should be considered.

Anticholinergic Adverse Reactions in Subjects with Moderate Renal Impairment:

Trospium is substantially excreted by the kidney. The effects of moderate renal impairment on systemic exposure are not known but systemic exposure is likely increased. Therefore, anticholinergic adverse reactions (including dry mouth, constipation, dyspepsia, urinary tract infection, and urinary retention) are expected to be greater in subjects with moderate renal impairment.

Elevation of liver enzymes:

Elevated liver enzymes have been reported in previous studies of xanomeline alone in Alzheimer's disease patients. It is notable however, the hepatic enzyme elevations were not observed in the Phase 1 studies in healthy volunteers and that the liver function test elevations observed in the Phase 2 schizophrenia study (KAR-004) with KarXT (a combination of xanomeline and trospium) were quite limited in contrast to the effects observed with xanomeline in the elderly Alzheimer's population. Moreover, even in the Alzheimer disease patients who experienced more hepatic enzyme elevations, the data demonstrate reversibility even with continued xanomeline treatment in those patients where there was sufficient follow-up data. Importantly, there were no Hy's law cases or elevations in total bilirubin to a value of >2X upper limit of reference range in either the xanomeline or KarXT datasets.

11.8 Pregnancy

WOCBP must have a negative pregnancy test at baseline (Day 0).

The investigator must notify the Sponsor (or designee) of any female subject or female partner of a male subject that becomes pregnant while participating in the study. Any known cases of pregnancy will be reported until the subject completes or withdraws from the study.

The pregnancy will be reported immediately by faxing/emailing a completed pregnancy report to the Sponsor (or designee) within 24 hours of knowledge of the event. The pregnancy will not be processed as an SAE; however, the investigator will follow-up with the subject until completion of the pregnancy and must assess the outcome in the shortest possible time, but not more than 30 days after completion of the pregnancy.

If a female subject becomes pregnant, the investigator must withdraw her from the study without delay. The subject must not receive any further doses of the KarXT. Upon discontinuation from the study, only those procedures that would not expose the subject to undue risk will be performed.

If the female subject or the female partner of the male subject is willing and able to consent to pregnancy follow-up, she will be followed until her pregnancy reaches term. Information regarding the pregnancy must only be submitted after obtaining written consent from the pregnant partner. The investigator will arrange counseling for the pregnant partner by a specialist to discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

The investigator should notify the Sponsor (or designee) of the pregnancy outcome by submitting a follow-up pregnancy report. If the outcome of the pregnancy involved spontaneous or therapeutic abortion (any congenital anomaly detected in an aborted fetus is to be documented), stillbirth, neonatal death, or congenital anomaly, the investigator will report the event by faxing/emailing a completed pregnancy report form to the Sponsor (or designee) within 24 hours of knowledge of the event. This event is considered as an SAE.

The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a subject is subsequently found to be pregnant after inclusion in the study, any pregnancy will be followed to term, and the status of mother and child will be reported to the Sponsor after delivery.

11.9 Overdose

The investigator must immediately notify the Sponsor of any occurrence of overdose with KarXT (total daily dose greater than 250/60 mg).

Signs and symptoms of overdose may vary considerably. They are usually manifested by increasing GI stimulation with epigastric distress, abdominal cramps, diarrhea and vomiting, excessive salivation, pallor, cold sweating, urinary urgency, blurring of vision, and eventually fasciculation and paralysis of voluntary muscles. Miosis, increases or decreases in blood pressure with or without bradycardia, and severe anxiety and panic may occur.

Supportive treatment should be used as indicated (artificial respiration, maintenance of airway, oxygen, etc). Atropine sulfate should be available for IV or intramuscular administration. Several doses ranging from 0.5 to 2.0 mg may be required. Epinephrine 0.1 to 1.0 mg subcutaneous may also be of value in overcoming severe cardiovascular or bronchoconstrictor responses.

Adverse events associated with overdoses should be reported on the eCRF.

11.10 Simpson-Angus Rating Scale

The SAS is an established instrument to measure drug-related extrapyramidal syndromes. It is a 10-item testing instrument used to assess gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, head dropping, glabella tap, tremor, and salivation. The range of scores is from 0 to 40 with increased scores indicating increased severity.

11.11 Barnes Rating Scale for Akathisia

The Barnes Rating Scale for akathisia is a rating scale used to assess the severity of drug-induced akathisia, or restlessness, involuntary movements and inability to sit still. The range of scores is 0 to 14, with higher scores indicating greater severity.[23]

11.12 Abnormal Involuntary Movement Scale

The AIMS is a rating scale that is used to measure involuntary movements know as tardive dyskinesia, which can sometimes develop as a side effect of long-term treatment with antipsychotic medications. It is a 12-item scale to assess orofacial, extremity, and truncal movements as well as the overall severity, incapacitation, and the subject's level of awareness of the movements. Items are scored from 0 (none) to 4 (severe). A higher score indicates more severe dyskinesia.

11.13 Columbia-Suicide Severity Rating Scale

The C-SSRS is a tool designed to systematically assess and track suicidal AEs (suicidal behavior and suicidal ideation) throughout the study.[24] The strength of this suicide classification system is in its ability to comprehensively identify suicidal events while limiting the over-identification of suicidal behavior. The scale takes approximately 5 minutes to administer. The C-SSRS will be administered by a trained rater at the site.

11.14 Functional Constipation Inquiry

Constipation refers to bowel movements that are infrequent or hard to pass.[25] The stool is often hard and dry.[26] Other symptoms may include abdominal pain, bloating, and feeling as if one has not completely passed the bowel movement.[27] The normal frequency of bowel movements in adults is between 3 per day and 3 per week.[25] Constipation will be defined per the Rome III criteria, as less than 3 bowel movements per week, Appendix 2 (Longswreth,1486,C3).[28]

The Bristol Stool Form Scale has been correlated with a change in intestinal function, and has been shown to be a useful tool in clinical practice and research.[29] A sample Bristol Stool Form Scale is located in Appendix 2.

As a measure of anticholinergic effects, at specified visits (Table 2), subjects will be asked whether they have experienced constipation per the ROME III criteria since the last visit, and if yes, whether the constipation required intervention. If the subject answers yes, sites are

instructed to ask subjects to provide event date and ensure event is documented as an AE and treatment is documented as concomitant medication. Subjects will not be required to collect and present their stool sample, nor will clinic staff be required to corroborate the subject assessment.

Additional attention can be given to other complaints as well including: straining with bowel movements, excessive time needed to pass a bowel movement, hard stools, pain with bowel movements secondary to straining, abdominal pain, abdominal bloating, and the sensation of incomplete bowel evacuation.[27, 30]

Treatment of constipation depends on the underlying cause and the duration that it has been present. For the purposes of constipation complaints during a clinical trial, the use of laxatives of a bulk forming agent, osmotic agent, stool softener, or lubricant type may be used.

As definitions of constipation are typically based on a history of at least a week, site physician discretion will be allowed for initiation of such treatments.

12 EFFICACY ASSESSMENTS

The Schedule of Assessments (Table 2) outlines the efficacy assessments to be performed throughout the study and their timing.

12.1 Positive and Negative Syndrome Scale

The PANSS is a clinician-administered scale used for measuring symptom severity of subjects with schizophrenia and is widely used in the study of antipsychotic therapy.[31] The PANSS rating form contains 7 positive symptom scales, 7 negative system scales, and 16 general psychopathology symptom scales. Subjects are rated from 1 to 7 on each symptom scale. The positive symptoms in schizophrenia are the excess or distortion of normal function such as hallucinations, delusions, grandiosity, and hostility, and the negative symptoms in schizophrenia are the diminution or loss of normal functions. It takes approximately 45 to 50 minutes to administer. PANSS total score is the sum of all scales with a minimum score of 30 and a maximum score of 210.

It is recommended, if at all possible, that the PANSS assessment should be performed before all the other scale assessments for all visits at which it is performed.

12.2 Clinical Global Impression-Severity

The CGI-S is a rating scale, completed independently by a clinician that is used to measure illness and symptom severity in subjects with mental disorders. It is used to rate the severity of a subject's illness at the time of assessment. The CGI-S modified asks the clinician 1 question: *"Considering your total clinical experience, how mentally ill is the subject at this time?"* The clinician's answer is rated on the following 7-point scale: 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill subjects.[32]

This rating is based upon observed and reported symptoms, behavior, and function in the past 7 days. As symptoms and behavior can fluctuate over a week, the score should reflect the average severity level across the 7 days.

13 PHARMACOKINETICS

13.1 Pharmacokinetic Sampling

13.1.1 PK Blood Samples and Timing

On Days 8, 14, 84, 168, and 280, a single sample will be collected during the subject's regularly scheduled study visit (see Table 2). On Day 8 the PK sample should be drawn within 1 to 2 hours post-dose whenever possible.

Approximately 4 mL of blood will be collected at each scheduled time point. The actual date and time of each blood sample collection will be recorded.

A single PK sample may be drawn if a relevant/significant AE is reported or if there is a dose adjustment. For ET that is related to an AE, collection of PK blood sample at the ET visit is recommended.

Details of PK blood sample collection, processing, storage, and shipping procedures will be provided in a separate laboratory manual.

13.2 Pharmacokinetic Analytical Methodology

The plasma concentration of trospium and xanomeline in PK samples will be measured using a validated bioanalytical method. Details of the method validation and sample analysis will be included with the final clinical study report.

14 EXPLORATORY ASSESSMENTS

The exploratory assessments cognition testing, prolactin levels, digital biomarkers, EMA PRO, and EMA VLMT will be performed at scheduled visits or study days, as per the Schedule of Assessments (Table 2).

14.1 Cognition Testing - Cambridge Neuropsychological Test Automated Battery

The computerized CANTAB provides an objective measure of cognitive function correlated to neural networks. A short cognitive battery measuring core cognitive domains of impairment in schizophrenia (ie, as per Brief Assessment of Cognition Schizophrenia key cognitive domains) will be employed for this study, and it will take approximately 30 minutes to complete. These CANTAB tests meet MATRICS workshop criteria.[33] Subjects will perform the test on a provisioned iPad with data immediately uploaded to the CANTAB Connect cloud-based platform (Wi-Fi permitting).

Cognition testing should not be done within 8 hours of receiving benzodiazepine or sleep medications.

Table 6. Cognitive Tests and Cognitive Domains Assessed by the Cambridge Neuropsychological Test Automated Battery

CANTAB Tests	MATRICS Cognitive Domain	Outcome Measures
Rapid visual information processing	Sustained attention/vigilance	**A' Prime:** Signal detection measure of how good the subject is at detecting the target sequence (string of three numbers); regardless of response tendency
Verbal recognition memory	Verbal memory and new learning	**Free Recall:** The total number of words that are correctly recalled from the presentation phase by the subject during the immediate free recall stage
Spatial Span	Working memory	**Forward Span Length:** The longest sequence of boxes successfully recalled by the subject
One-touch stockings of Cambridge	Executive Function Planning/Problem Solving	**Problems Solved on First Choice:** The total number of assessed trials where the subject chose the correct answer on their first attempt

Abbreviation: CANTAB = Cambridge Neuropsychological Test Automated Battery

14.2 Change in Prolactin

Blood samples to assess the change in prolactin levels will be obtained on scheduled visits as specified in Table 2. Prolactin sample is optional when sites are using local labs.

14.3 Digital Biomarkers of Schizophrenia (US only)

Study subjects will be performing brief smartphone-based assessments using the AiCure application mentioned in Section 10.2.1. Video and audio of participant behavior captured during these assessments will be used to calculate visual and auditory markers of schizophrenia symptomatology. These digital biomarkers will be used as exploratory efficacy endpoints to measure change from baseline in disease severity. The following exploratory endpoints will be collected:

- Overall emotional expressivity
- Positive emotional expressivity
- Negative emotional expressivity
- Audio intensity / speech volume Fundamental frequency of voice
- Formant frequencies of voice
- Vocal jitter
- Vocal shimmer
- Pause lengths during speech
- Lexical diversity
- Rate of speech
- Euclidean head movement
- Rotational head movement

14.4 EMA Wellness Assessments

14.4.1 EMA Wellness – EMA PRO (US only)

EMA is an ambulatory data collection technique that allows the real-time in vivo assessment of functioning behaviors. In the present study, EMA Patient Reported Outcomes (PRO) will be used to assess the subject's functioning associated to negative symptoms and psychotic symptoms in schizophrenia through the use of smartphones for subjects enrolled at US sites only.

EMA PRO surveys are multiple choice questions about the subject's current location, if they are alone or with others, and activities and moods in the last hour. A pop-up visualization will signal participants, 3 times per day for 7 days, to respond to very brief (e.g., 3 minutes) questionnaires about their activities, mood, and symptom experiences during the last hour, per the Schedule of Assessments (Table 2). An abbreviated EMA PRO survey, collecting only information on the subject's location, alone or with others, and activities and moods will be given 3 times per day for 3 days starting on Day 4 and Day 15. Daily assessment times will be adjusted to accommodate each subject's typical sleep and wake schedules.

14.4.2 EMA Wellness - VLMT (US only)

Cognitive insight assessment will be conducted through testing on the Verbal Learning and Memory Test (VLMT), which will be completed by subjects enrolled at US sites only. This assessment will be performed at home on a cellular device 1 time per day for 2 days every 28 days beginning on Day 32. During each VLMT administration, subjects will be presented with a list of 6- or 12-words over in 2 separate trials each lasting 30 seconds. Immediately following each exposure to the list, subjects will be shown target and recognition foil words one-by-one and asked to indicate whether or not the word appeared on the list.

In order to examine response bias and the ability to self-evaluate memory performance, immediately after each recognition trial, the subjects will be asked to indicate how many words they believe that they got correct. They will also be asked how well they did as compared to the previous trial and at the end of the 2 trials they will be asked if they improved over the 2 learning trials.

14.4.3 Data Collected on EMAW Platform

Data are encrypted and uploaded to secure servers whenever the phone is connected to Wi-Fi or if cellular data is available. If a Wi-Fi and cellular data are unavailable, EMA response data will be transferred during in-clinic visits.

During each EMA PRO, subjects will be asked about their location (home vs away and where if away); they will also be asked if they are alone or with others, and about their activities, symptoms of schizophrenia, and moods in the last hour.

Data collected during the VLMT include the identification of target words and rejections of foils. The participants will also provide an immediate estimate of their memory task performance as soon as each recognition trial is over.

15 STATISTICAL ANALYSIS

A statistical analysis plan (SAP) will be prepared after the protocol is approved. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. The SAP will serve as a complement to the protocol and supersedes it in case of differences.

The statistical evaluation will be performed using SAS® software version 9.4 or higher (SAS Institute, Cary, NC). All data will be listed, and summary tables will be provided. Summary statistics will be presented by dose group. For continuous variables, data will be summarized with the number of subjects (N), mean, standard deviation, median, minimum, and maximum by treatment group. For categorical variables, data will be tabulated with the number and proportion of subjects for each category by treatment group. No statistical hypothesis testing will be performed.

15.1 Determination of Sample Size

As the primary objective of this study is to assess the long-term safety and tolerability of KarXT, the number of subjects anticipated is based on the number of subjects recruited into and completing the acute studies (KAR-007, KAR-009) and meeting the eligibility requirements for KAR-008.

15.2 Analysis Populations

Enrolled population: All subjects who have given informed consent for KAR-008.

Safety population: All subjects who receive at least 1 dose of KarXT during the current study will be included in the safety population and will be used in the safety analysis.

Modified ITT (mITT) population: All subjects who are enrolled, received at least 1 dose of KarXT, and have a valid PANSS assessment at KAR-008 baseline will be included in the mITT population and will be used in the efficacy analysis.

PK population: All subjects who have received at least 1 dose of KarXT and have at least 1 measurable plasma concentration of KarXT will be included in the PK population.

15.3 Safety Analysis

Safety endpoints will be summarized for all subjects in the Safety population. The presentation of safety data will be based on the treatment received in KAR-008.

All reported AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.1 or higher. The incidence of TEAEs (defined as events with an onset date on or after the first dose of KarXT) will be summarized by System Organ Class and Preferred Term. All AEs will be listed by subject, along with information regarding onset, duration, relationship and severity to KarXT, action taken with KarXT, treatment of event, and outcome.

Orthostatic vital signs, clinical laboratory data, prolactin levels, ECG parameters, and physical examinations will be summarized using descriptive statistics, including observed and change from baseline values, as well as numbers of subjects with values outside limits of the normal range at each time point. Similar descriptive summaries will be provided for C-SSRS, SAS, BARS, AIMS, body weight, BMI, and waist circumference.

15.4 Efficacy Analysis

Efficacy analyses will be summarized based on the mITT population. The summaries described in this section will provide data on maintenance of effect of open-label KarXT over 52 weeks. As these variables are summarized over time and the initial values can be impacted by the treatment received in the acute study, the presentation will use a combination of acute/extension study treatment groups, which is intended to provide perspective on the change in these values from the acute study through the treatment period of KAR-008. Tabular presentations will display descriptive statistics for Baseline of the acute study and the observed and change from baseline study results by scheduled visit for KAR-008.

Responder efficacy variables (PANSS responders) will be summarized descriptively. Response will be derived relative to the acute study Baseline assessment.

Continuous efficacy variables based on the change from baseline (PANSS, CGI-S) will be summarized using descriptive statistics by scheduled visit. Tabular presentations will display descriptive statistics for the Baseline of the acute study and the observed and change from baseline results by scheduled visit for KAR-008. Figures for selected variables will also be generated in order to demonstrate the kinetics of response over time.

15.5 Pharmacokinetic Analysis

The PK evaluation will rely on an existing population PK model for KarXT in subjects with schizophrenia. The plasma concentrations of xanomeline and trospium measured in this study will be overlaid onto distributions of concentrations predicted by the population PK model developed from KAR-007 and KAR-009 data. Percentages of measured concentrations in the current study that lie within, above, and below the 90% prediction interval of concentrations predicted by the model will be calculated.

Details of the PK analysis will be described in the SAP.

15.6 Exploratory Analysis

The following will be summarized using descriptive statistics: change in cognition using CANTAB; digital biomarkers of schizophrenia; EMA PRO and EMA VLMT.

Further details will be provided in the SAP.

15.7 Interim Analysis

No interim analysis is planned for this study.

15.8 Handling of Missing Data

For responder efficacy variables (PANSS responders), missing data may be handled by non-responder imputation, meaning that subjects who discontinue early or who have missing data at a given time point are imputed as though they did not achieve the given response. Supportive summaries will be based on observed case data.

For continuous efficacy variables based on the change from baseline (PANSS, CGI-S), summaries will be based on observed case data.

Additional methods of missing data imputation may be explored and will be outlined in the SAP.

16 STUDY MANAGEMENT

16.1 Approval and Consent

16.1.1 Regulatory Guidelines

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the US Code of Federal Regulations (CFR), in compliance with International Council for Harmonisation (ICH) and good clinical practice (GCP) guidelines, and all applicable local, state and federal government regulations and laws.

16.1.2 Institutional Review Board/Independent Ethics Committee

Conduct of the study must be approved by an appropriately constituted IEC/IRB. Approval is required for the study protocol, protocol amendments (if applicable), IB, ICFs, recruitment material and subject information sheets and other subject-facing material.

16.1.3 Informed Consent

For each study subject, written informed consent will be obtained before any protocol-related activities. As part of this procedure, the PI or designee must explain orally and in writing the nature of the study, its purpose, procedures, expected duration, alternative therapy available, and the benefits and risks involved in study participation. The subject should be informed that they may withdraw from the study at any time, and the subject will receive all information that is required by local regulations and guidelines for ICH. The PI will provide the Sponsor or its representative with a copy of the IEC-/IRB-approved ICF before the start of the study.

The ICF should be revised whenever there are substantial changes to procedures or when new information becomes available that may affect the willingness of the subject to participate. Revisions to the consent form required during the study must be approved by the Sponsor and IEC/IRB, and a copy of the revised consent form is provided to the Sponsor. For any updated or revised consent forms, the subjects must be re-consented for continued participation in the study.

A pregnant partner consent form should be obtained before collecting any data from a female pregnant partner of a male subject, if she becomes pregnant during the course of the study or within 1 week of the last dose of KarXT.

A caregiver consent must be obtained (Ukraine only) before collecting any data from a caregiver pertaining to him or her and the subject.

Subject Registry (US only)

Clinical trial registries, such as clinical trial subject database (CTSdatabase) and Verified Clinical Trials (VCT) seek to reduce duplicate enrollment by identifying potential protocol violations and duplicate subjects before randomization. At the time of providing the informed consent for the initial KAR-007 or -009 study (US Only), the investigator or designee will have

explained the IRB/IEC-approved Subject Database Authorization to the subject and witnessed the signature. That executed authorization form remains in effect for KAR-007 and KAR-008 or KAR-009 and KAR-008 study participation.

At the beginning of screening for KAR-007 or KAR-009 (US only), following consents execution and subject number assignment and before other study procedures, site staff that had received training and login information access (www.subjectregistry.com) to the database entered the subject study ID number and authorized subject identifiers. Two reports, one from CTS and one from VCT, detailing any potential protocol violations or dual enrollment attempts were generated and were printed for source documentation. The reports detailed each protocol violation detected and specific washout period dates where applicable.

Throughout the initial KAR-007 or KAR-009 study, and during this open label extension study, tracking of actively enrolled subjects will continue based on updates by coordinators in the interactive response system. At the last subject contact, CTSdatabase and VCT staff will automatically close out the subject (safety follow-up, ET, or completer) based on interactive response system (IXRS).

16.2 Data Handling

Any data to be recorded directly on the eCRFs (to be considered as source data) will be identified at the start of the study. Data reported on the eCRF that are derived from source documents should be consistent with the source documents, or the discrepancies must be explained. See also Section 16.3.

Clinical data will be entered by site personnel on eCRFs for transmission to the Sponsor. Data on eCRFs transmitted via the web-based data system must correspond to and be supported by source documentation maintained at the study site unless the study site makes direct data entry to the databases for which no other original or source documentation is maintained. In such cases, the study site should document which eCRFs are subject to direct data entry and should have in place procedures to obtain and retain copies of the information submitted by direct data entry. All study forms and records transmitted to the Sponsor must only include coded identifiers such that directly identifying personal information is not transmitted. The primary method of data transmittal is via the secure, internet-based electronic data capture (EDC) system maintained by Syneos Health. Access to the EDC system is available to only authorized users via the study's secure internet web site, where a user unique assigned username and password are required for access.

Any changes made to data after collection will be made through the use of the EDC system. Electronic CRFs will be considered complete when all missing and/or incorrect data have been resolved.

16.3 Source Documents

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. The investigator will provide direct access to source documents and/or source data in the facilitation of trial-related monitoring, audits, review by IECs/IRBs, and regulatory inspections.

The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, not obscure the original entry, and be explained if necessary.

Data recorded on source documents will be transcribed onto eCRFs. Copies of completed eCRFs will be provided to the Sponsor and the sites at the end of the study. The completed eCRFs will be retained by the investigator.

16.4 Record Retention

Study records and source documents must be preserved for at least 15 years after the completion or discontinuation of/withdrawal from the study, at least 2 years after the drug being studied has received its last approval for sale, or at least 2 years after the drug development has stopped, and in accordance with the applicable local privacy laws, whichever is the longer time period.

The investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of subject health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR, Parts 160 and 164 (the HIPAA of 1996 Privacy Regulation). The investigator shall ensure that study subjects authorize the use and disclosure of protected health information in accordance with HIPAA Privacy Regulation and in a form satisfactory to the Sponsor.

16.5 Monitoring

The study will be monitored according to the KAR-008 monitoring plan to ensure that it is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements.

Monitoring visits may include on-site or remote visits and may also utilize periodic telephone contacts. The PI will assure they and adequate site personnel are available throughout the study to collaborate with clinical monitors. Clinical monitors must have direct access to source documentation in order to check the completeness, clarity, and consistency of the data recorded in the eCRFs for each subject.

The investigator will make available to the clinical monitor all source documents and medical records necessary to review protocol adherence and eCRFs. In addition, the investigator will work closely with the clinical monitor and as needed, provide them appropriate evidence that the

study is being conducted in accordance with the protocol, applicable regulations, and GCP guidelines.

16.6 Quality Control and Quality Assurance

The Sponsor or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, security, and reliability of the study data presented to the Sponsor lies with the investigator generating the data.

The Sponsor or its designee will arrange audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the protocol, standard operating procedures, GCP, and all applicable regulatory requirements. Audits will be independent of and separate from the routine monitoring and quality control functions. Quality assurance procedures will be performed at study sites and during data management to assure that safety and efficacy data are adequate and well documented.

16.7 Protocol Amendment and Protocol Deviation

16.7.1 Protocol Amendment

Amendments to the protocol that entail corrections of typographical errors, clarifications of confusing wording, changes in study personnel, and minor modifications that have no effect on the safety of subjects or the conduct of the study will be classed as administrative amendments and will be submitted to the IEC/IRB for information only. Syneos Health will ensure that acknowledgement is received and filed. Amendments that are classed as substantial amendments must be submitted to the appropriate regulatory authorities and the IECs/IRBs for approval and will not be implemented at sites until such approvals are received, other than in the case of an urgent safety measure.

16.7.2 Protocol Deviations

Should a protocol deviation occur, the Sponsor must be informed as soon as possible. Protocol deviations and/or violations and the reasons they occurred will be included in the clinical study report. Reporting of protocol deviations to the IEC/IRB and in accordance with applicable regulatory authority mandates is an investigator's responsibility.

- All protocol deviations will be tracked in the Clinical Trial Management System. Deviations considered major will be identified as such before study unblinding during medical monitor periodic review.

Major protocol deviations will be tabulated including the frequency and percentage of subjects with each type of deviation by treatment group.

16.8 Ethical Considerations

This study will be conducted in accordance with this protocol, the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the CFR; and in compliance with GCP guidelines.

IECs/IRBs will review and approve this protocol and the ICF. All subjects and/or caregivers (Ukraine only) are required to give written informed consent before participation in the study.

16.9 Financing and Insurance

Before the study commences, the Sponsor (or its designee) and the investigator (or the institution, as applicable) will agree on costs necessary to perform the study. This agreement will be documented in a financial agreement that will be signed by the investigator (or the institution signatory) and the Sponsor (or its designee).

The investigator is required to have adequate current insurance to cover claims for negligence and/or malpractice (US only). The Sponsor will provide no-exclusion insurance coverage for the clinical study as required by national regulations.

16.10 Publication Policy/Disclosure of Data

Both the use of data and the publication policy are detailed within the clinical study agreement. Intellectual property rights (and related matters) generated by the investigator and others performing the clinical study will be subject to the terms of a clinical study agreement that will be agreed between the institution and the Sponsor or their designee. With respect to such rights, the Sponsor or its designee will solely own all rights and interests in any materials, data, and intellectual property rights developed by investigators and others performing the clinical study described in this protocol, subject to the terms of any such agreement. In order to facilitate such ownership, investigators will be required to assign all such inventions either to their institution or directly to the Sponsor or its designee, as will be set forth in the clinical study agreement.

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18 APPENDICES

Appendix 1: Contraception Guidelines

Female subjects of childbearing potential with a non-sterilized male sexual partner must agree to use at least 1 highly effective method of contraception (eg, hormonal or double barrier method of birth control, or intrauterine device) beginning >30 days before receiving study drug on Day 1 and continuing until 30 days after the End of Study (EOS) Visit. If oral contraceptives are used, the subject must have been on a stable dose for ≥6 months.

A woman is considered to be WOCBP following menarche and until becoming postmenopausal, unless she is permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy [22]. Female subjects who are postmenopausal, which is defined as 12 consecutive months with no menses without an alternative medical cause, must have been postmenopausal for >1 year if they wish to not use contraceptives. Postmenopausal status must be confirmed by a test of the subject's follicle-stimulating hormone (FSH) level which must be elevated and consistent with postmenopausal levels (ie, >40 IU/L); otherwise, these subjects must agree to use contraceptives listed below. Female subjects who are surgically sterile (ie, hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) will not need to undergo the FSH level test.

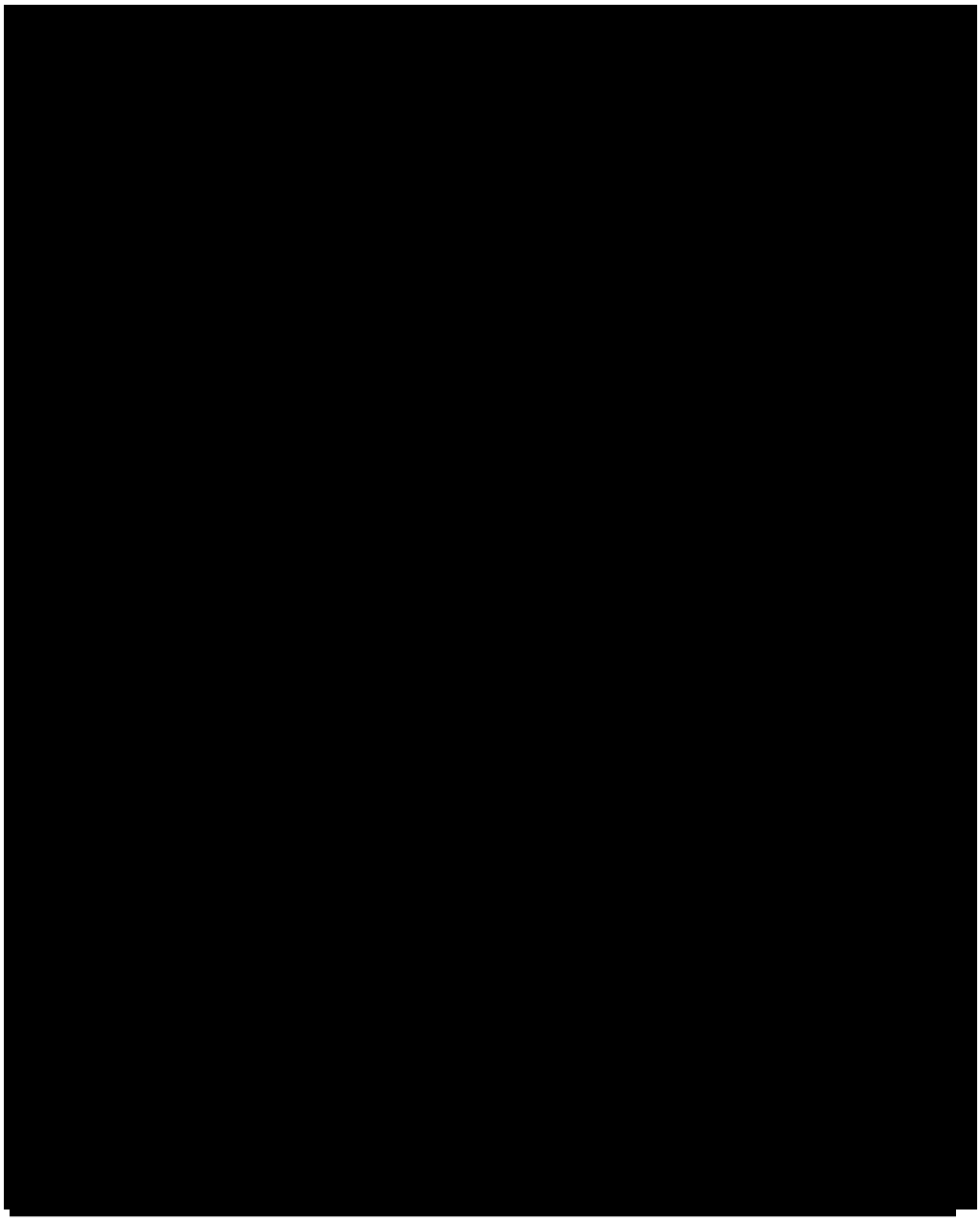
A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

Highly effective methods of contraception are those that have a failure rate of <1% (when implemented consistently and correctly) and include the following:

- combined (containing estrogen and progestogen) hormonal contraception associated with inhibition of ovulation (administration may be oral, intravaginal, or transdermal)
- progestogen-only hormonal contraception associated with inhibition of ovulation (administration may be oral, injectable, or implantable)
- intrauterine device
- intrauterine hormone-releasing system
- bilateral tubal ligation or occlusion
- vasectomy (provided that the male has a medical assessment of surgical success)

All subjects will be strongly advised that they (or the female partners of male subjects) should not become pregnant before receiving study drug on Day 1 and continuing until 30 days after the End of Study Visit. A female subject will be advised that she must report immediately to the study site for pregnancy testing and appropriate management in the event that she may be pregnant.

Appendix 2: Functional Constipation Inquiry



1 FINAL CLINICAL STUDY PROTOCOL

Karuna Therapeutics

Protocol Title: An Open-label Extension Study to Assess the Long-term Safety, Tolerability, and Efficacy of KarXT in Subjects with DSM-5 Schizophrenia

Protocol Number: KAR-008

IND Number:	127471
EudraCT Number:	Not applicable
Name of Investigational Product:	KarXT
Phase of Development:	Phase 3
Indication:	Schizophrenia
Sponsor:	Karuna Therapeutics 99 High St. Floor 26 Boston, MA 02110 Tel: [redacted] Email: [redacted]
Protocol Version:	Version 4.0
Protocol Date:	11 Jan 2022

PROTOCOL APPROVAL SIGNATURES

Protocol Title: An Open-label Extension Study to Assess the Long-term Safety, Tolerability, and Efficacy of KarXT in Subjects with DSM-5 Schizophrenia

Protocol Number: KAR-008

This study will be conducted in compliance with the clinical study protocol (and amendments), International Council for Harmonisation (ICH) guidelines for current Good Clinical Practice (GCP), and applicable regulatory requirements.

Sponsor Signatory

[redacted]
Karuna Therapeutics

DocuSigned by:
[redacted]
Signature
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 1/20/2022 | 6:54:27 AM PST
[redacted]
Date

[redacted]
Karuna Therapeutics

DocuSigned by:
[redacted]
Signature
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 1/20/2022 | 7:09:57 AM PST
[redacted]
Date (DD-Mmm-YYYY)

Contract Research Organization Signatory

[redacted]
Syneos Health

DocuSigned by:
[redacted]
Signature
Signer Name: [redacted]
Signing Reason: I have reviewed this document
Signing Time: 1/20/2022 | 7:15:23 AM PST
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Date

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Signer Name: [redacted]
Signing Reason: I have reviewed this document
Signing Time: 1/20/2022 | 10:32:37 AM EST
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Date (DD-Mmm-YYYY)

INVESTIGATOR SIGNATURE PAGE

Protocol Title: An Open-label Extension Study to Assess the Long-term Safety, Tolerability, and Efficacy of KarXT in Subjects with DSM-5 Schizophrenia

Protocol Number: KAR-008

Confidentiality and Current Good Clinical Practice (GCP)/E6(R2) Compliance Statement

- I, the undersigned, have reviewed this protocol (and amendments), including appendices, and I will conduct the study as described in compliance with this protocol (and amendments), and relevant International Council for Harmonisation (ICH) guidelines including GCP and applicable regulatory requirements.
- I am thoroughly familiar with the appropriate use of the KarXT, as described in this protocol and any other information provided by Karuna Therapeutics including, but not limited to, the current investigator's brochure.
- Prior to initiating the trial, I will provide the independent ethics committee (IEC)/institutional review board (IRB) all items subject to review and will obtain a written and dated approval/favorable opinion. Once the protocol has been approved by the IEC/IRB, I will not modify this protocol without obtaining prior approval of Karuna Therapeutics and of the IEC/IRB. I will submit the protocol amendments and/or any informed consent form modifications to Karuna Therapeutics and the IEC/IRB, and approval will be obtained before any amendments are implemented.
- I ensure that all persons or party assisting me with the study are adequately qualified and informed about the Karuna Therapeutics KarXT and of their delegated study-related duties and functions as described in the protocol. I will supervise these delegated persons or parties in the conduct of this trial.
- I ensure that source documents and trial records that include all pertinent observations on each of the site's trial subjects will be attributable, legible, contemporaneous, original, accurate, and complete.
- I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all case report forms, laboratory samples, or source documents forwarded to the Sponsor. Clinical information may be reviewed by the Sponsor or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.
- Information developed in this clinical study may be disclosed by Karuna Therapeutics to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

<Name>

<Title>

Investigator Signature

Date (DD-Mmm-YYYY)

Institution

2 SYNOPSIS

Title of Study:	An Open-label Extension Study to Assess the Long-term Safety, Tolerability, and Efficacy of KarXT in Subjects with DSM-5 Schizophrenia
Protocol Number:	KAR-008
Investigators/Study Sites:	Approximately 30 study sites in the United States and 10 study sites in Ukraine
Phase of Development:	Phase 3
Objective(s):	**Primary Objective:** The primary objective of the study is to assess the long-term safety and tolerability of KarXT in subjects with a Diagnostic and Statistical Manual-Fifth Edition (DSM-5) diagnosis of schizophrenia. **Secondary Objectives:** The secondary objective of this study is to assess the long-term efficacy and evaluate plasma concentrations of xanomeline and trospium after administration of KarXT in adults with a DSM-5 diagnosis of schizophrenia: • To evaluate the reduction in Positive and Negative Syndrome Scale (PANSS) total score • To evaluate the reduction in PANSS positive score • To evaluate the improvement in Clinical Global Impression Severity (CGI-S) results • To evaluate the reduction in PANSS negative score • To evaluate the reduction in PANSS Marder Factor negative symptoms score **Exploratory Objectives:** The exploratory objectives of this study are: • To evaluate cognition with the Cambridge Neuropsychological Test Automated Battery (CANTAB) • To evaluate prolactin levels after administration of KarXT • To characterize outcomes obtained from digital biomarkers, ecological momentary assessment administered patient reported outcomes (EMA PRO), and an EMA administered verbal learning and memory test (EMA VLMT) in schizophrenia
Study Endpoints:	**Primary safety endpoint:** The primary safety endpoint is the incidence of treatment-emergent adverse events (TEAEs) **Secondary safety endpoints:** The secondary safety endpoints of the study are: • Incidence of serious TEAEs • Incidence of TEAEs leading to withdrawal

	Secondary efficacy endpoints: The secondary efficacy endpoints of the study are: • Change from baseline in PANSS total score at Week 52 • Change from baseline in PANSS positive score at Week 52 • Change from baseline in PANSS negative score at Week 52 • Change from baseline in PANSS Negative Marder Factor score at Week 52 • Change from baseline in CGI-S score at Week 52 • Percentage of PANSS responders (a ≥30% reduction in PANSS total score) at Week 52 **Other Endpoints:** <u>Safety endpoints</u>: The other safety endpoints of the study are: • Spontaneously reported adverse events of special interest (AESIs) • Spontaneously reported procholinergic and anticholinergic symptoms • Change from baseline in Simpson-Angus Rating Scale (SAS) • Change from baseline in Barnes Rating Scale for Akathisia (BARS) • Change from baseline in Abnormal Involuntary Movement Scale (AIMS) • Change from baseline in body weight, body mass index (BMI), waist circumference • Change from baseline in orthostatic vital signs (supine and standing after 2 minutes): blood pressure (systolic and diastolic) and heart rate • Change from baseline in clinical laboratory assessments (hematology, clinical chemistry, coagulation, urinalysis, and drug screen) • Change from baseline in 12-lead electrocardiogram (ECG) • Change from baseline in physical examination • Suicidal ideation scale with the use of Columbia-Suicide Severity Rating Scale (C-SSRS) <u>Pharmacokinetic Endpoint</u>: • Comparison of the plasma concentrations of xanomeline and trospium measured in this study to the plasma concentrations predicted by a population pharmacokinetic (PK) model of studies KAR-007 and KAR-009 <u>Exploratory Endpoints</u>: The exploratory endpoints of the study are: • Change from baseline in cognition measuring core domains of impairment in schizophrenia using CANTAB • Change from baseline in prolactin levels • Observed digital biomarkers of schizophrenia (US only) • Observed EMA PRO in schizophrenia (US only) • Observed cognitive insight using EMA VLMT in schizophrenia (US only)

Study Design:	This is a Phase 3 multicenter, 53-week, outpatient, open-label extension (OLE) study to evaluate the long-term safety, tolerability, and efficacy of KarXT in subjects with DSM-5 schizophrenia who previously completed the treatment period of one of the two Phase 3 double-blind studies, KAR-007 or KAR-009. The study consists of a 52-week OLE treatment phase and a 7-day (±3 days) safety follow-up/end-of-study visit after the last KarXT dose for subjects who complete the treatment phase and those who prematurely discontinue from the study. After written informed consent, subjects who have completed the KAR-007 or KAR-009 Phase 3 acute study and received the last dose of the study drug in that trial will be rolled over into the current OLE study. The assessments performed on Visit 10 (Day 35) of studies KAR-007 or KAR-009 will be considered as baseline assessments along with any additional procedures that will be performed on Day 0 of the current study. Any scheduled Day 0 assessments that were not completed on Day 35 of the acute study (KAR-007 or KAR-009) must be completed on Day 0 of the current study. It is preferable that Baseline/Day 0 procedures of the current study be completed on the same day as Day 35 of the acute study after all Visit 10 (Day 35) procedures of the prior study KAR-007 or KAR-009 have been completed. However, with medical monitor approval, an extension of up to 3 days can be granted to complete Baseline/Day 0 procedures. This extension cannot be completed inpatient. With medical monitor approval, participants may be permitted to complete the first 3 days (Visit 1/Day 1 to Visit 2/Day 3) of KAR-008 on the inpatient unit. Twice-daily dosing with KarXT will commence in the morning of Day 1. Subjects who did not complete the full treatment period, or who early terminated study KAR-007 or KAR-009, will not be eligible to enroll in this long-term extension study. Approximately 350 subjects are planned to be enrolled in this study (aged 18 to 65 years) across approximately 30 study sites in the United States and 10 study sites in Ukraine. In this OLE study, all subjects will receive KarXT for up to 52 weeks. Regardless of treatment assignment in the preceding Phase 3 acute study (KAR-007 or KAR-009), all subjects will start on a lead-in dose of KarXT 50/20 (50 mg xanomeline/20 mg trospium) 2 times per day (BID) for the first 2 days (Days 1 and 2), followed by KarXT 100/20 BID for the remainder of Week 1 (Days 3 to 7). At Visit 3 (Day 8), dosing will be titrated upwards to KarXT 125/30 BID unless the subject is continuing to experience adverse events (AEs) from the previous dose of KarXT 100/20 BID. All subjects who are increased to KarXT 125/30 BID, depending on tolerability, will have the option to return to KarXT 100/20 BID. Re-escalation to 125/30 BID or re-titration in cases in which the subject has been off KarXT for a longer period of time (at least a week) is allowed and will require a discussion between the principal investigator and the medical monitor. Additional changes to KarXT dosing (e.g., temporary dose reductions) may be permitted as clinically indicated upon approval by the medical monitor. Beginning after Visit 9/Day 84, interim visits will be completed with flexibility between in-clinic visits, and approximately once every 4 weeks thereafter. Whenever possible, interim visits should be conducted by telemedicine; however, sites will have the option to schedule on-site interim

	visits, and are encouraged to use additional unscheduled visits as necessary, to facilitate subject retention and ensure adherence to study objectives. A safety follow-up/end-of-study visit (Visit 30/Day 371 ±3 days) will be performed for all subjects after the last dose of KarXT. An Independent Safety Monitoring Committee will be responsible for periodically reviewing the safety data from this study and confirming that the study may continue.
Study Population:	**Inclusion Criteria:** Individuals must meet all of the following criteria to be included in the study: 1. Subject is aged 18 to 65 years, at time of enrollment into the preceding acute study (KAR-007 or KAR-009). 2. Subject is capable of providing informed consent. 3. A signed informed consent form must be provided before any study assessments are performed. • Subject must be fluent in (oral and written) English (United States only) or local language (Ukraine only) to consent. 4. Subject has completed the treatment period on study drug (through Day 35 -2 days) of studies KAR-007 or KAR-009. 5. Subject resides in a stable living situation, in the opinion of the investigator. 6. Subject has an identified, reliable informant/caregiver willing to be able to address some questions related to certain study visits, if needed. An informant/caregiver may not be necessary if the subject has been the patient of the investigator for ≥1 year. 7. Women of childbearing potential (WOCBP) or men whose sexual partners are WOCBP must be willing and able to adhere to the contraception guidelines as defined in Section 8.4.1 and Appendix 1. **Exclusion Criteria:** Subjects will be excluded from the study if 1 or more of the following criteria is/are applicable: 1. Risk for suicidal behavior during the study as determined by the investigator's clinical assessment and C-SSRS as confirmed by the following: a. Subject answers "Yes" to "suicidal ideation" Item 4 (active suicidal ideation with some intent to act, without specific plan) or Item 5 (active suicidal ideation with specific plan and intent) on the C-SSRS. b. Nonsuicidal self-injurious behavior is not exclusionary. 2. Any clinically significant abnormality, including any finding(s) from the physical examination, vital signs, ECG, or laboratory test at the end-of-treatment visit of Studies KAR-007 or KAR-009 that the investigator, in consultation with the medical monitor, would consider to jeopardize the safety of the subject. 3. Female subject is pregnant, breast feeding or planning to become pregnant during the course of the study. 4. If, in the opinion of the investigator (and/or Sponsor), subject is unsuitable for enrollment in the study or subject has any finding that, in the view of the investigator (and/or Sponsor), may compromise the

	safety of the subject or affect his/her ability to adhere to the protocol visit schedule or fulfill visit requirements. 5. Subjects with extreme concerns relating to global pandemics such as coronavirus disease 2019 (COVID-19) that preclude study participation. 6. Risk of violent or destructive behavior. 7. Subjects participating in another investigational drug or device trial or planning on participating in another clinical trial during the course of the study.
Planned Sample Size:	Approximately 350 subjects are planned to be enrolled in this study.
Investigational Therapy:	1. Fixed dose KarXT 50/20 BID (50 mg xanomeline/20 mg trospium) oral (Days 1 to 2) 2. Fixed dose KarXT 100/20 BID (100 mg xanomeline/20 mg trospium) oral (Days 3 to 7) 3. Fixed dose KarXT 125/30 BID (125 mg xanomeline/30 mg trospium) oral (Days 8 to 364, if tolerated)
Reference Therapy:	Not applicable.
Treatment Duration:	Total study duration is up to 53 weeks, including a 52-week treatment phase and a 7-day follow-up/end-of-study phase.
Safety assessments:	Spontaneous AEs including AESIs; procholinergic and anticholinergic symptoms, serious AEs (SAEs) and AEs leading to discontinuation of KarXT; SAS; BARS; AIMS; body weight; BMI; waist circumference; orthostatic vital signs; clinical laboratory assessments (hematology, clinical chemistry, coagulation, urinalysis, and drug screen); 12-lead ECG; physical examination; and C-SSRS will be evaluated throughout the study as scheduled.
Efficacy assessments:	PANSS total score, PANSS positive score, PANSS negative score, PANSS Negative Marder Factor score, and CGI-S score will be evaluated at scheduled visits.
Pharmacokinetic assessment:	Blood samples will be collected at scheduled visits for bioanalysis of plasma concentrations of xanomeline and trospium, and will be compared to the plasma concentrations predicted by a population pharmacokinetic (PK) model of studies KAR-007 and KAR-009.
Exploratory assessments	Cognition testing using CANTAB; prolactin levels; digital biomarkers of schizophrenia; EMA PRO and EMA VLMT will be evaluated during scheduled visits or on specified study days.
Statistical Methods and Planned Analyses:	Study Populations: Enrolled population: All subjects who have given informed consent for KAR-008. Safety population: All subjects who receive at least 1 dose of KarXT during the current study will be included in the safety population and will be used in the safety analysis. Modified ITT (mITT) population: All subjects who are enrolled, received at least 1 dose of KarXT during the current study, have a valid post-baseline PANSS assessment will be included in the mITT population and will be used in the efficacy analysis.

	PK population: All subjects who have received at least 1 dose of KarXT and have at least 1 measurable plasma concentration in the current study will be included in the PK population. The primary safety endpoint of the study is the incidence of TEAEs. Secondary safety endpoints are the incidence of serious TEAEs and the incidence of TEAEs leading to withdrawal of KarXT. The secondary efficacy endpoints are change from baseline to Week 52 in the PANSS total score, PANSS positive score, PANSS negative score, PANSS Negative Marder Factor score, CGI-S score, and the percentage of PANSS responders at Week 52. The exploratory endpoints of the study are change from baseline in cognition (CANTAB), prolactin levels, digital biomarkers, EMA PRO, and EMA VLMT. Descriptive statistics will be used to provide an overview of the safety and efficacy results. For continuous parameters, descriptive statistics will include n, mean, median, standard deviation, minimum and maximum; For categorical parameters, the number and percentage of subjects in each category will be presented. The denominator for percentages will be based on the number of subjects appropriate for the purposes of analysis. No statistical hypothesis testing will be performed.

3 TABLE OF CONTENTS

3.1 List of In-text Tables

3.2 List of In-text Figures

4 LIST OF ABBREVIATIONS

Abbreviation	Definition
AD	Alzheimer's disease
AE	adverse event
AESI	adverse event of special interest
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
APD	antipsychotic drug
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{0-24}	area under the plasma concentration-time curve from 0 to 24 hours
BACS	Brief Assessment of Cognition in Schizophrenia
BARS	Barnes Akathisia Rating Scale
BID	twice daily
BMI	body mass index
BP	blood pressure
CANTAB	Cambridge Neuropsychological Test Automated Battery
CFR	Code of Federal Regulations
CGI-S	Clinical Global Impression–Severity
C_{max}	maximum plasma concentration
CNS	central nervous system
COVID-19	coronavirus disease 2019
C-SSRS	Columbia-Suicide Severity Rating Scale
DSM-5	Diagnostic and Statistical Manual–Fifth Edition
EDC	electronic data capture
ECG	Electrocardiogram
EOS	end of study
EOT	end of treatment
ET	early termination
eCRF	electronic case report form
EMA	Ecological Momentary Assessment
EMAW	Ecological Momentary Assessment Wellness
EPS	extrapyramidal symptoms

Abbreviation	Definition
ET	early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
HIPAA	Health Insurance Portability Accountability Act
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	interactive web response system
IXRS	interactive response system
MCC	microcrystalline cellulose
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini International Neuropsychiatric Interview
mITT	modified intent-to-treat
MMRM	mixed model repeated measures
OLE	open-label extension
PANSS	Positive and Negative Syndrome Scale
PI	principal investigator
PK	pharmacokinetic(s)
PRO	patient reported outcome
SAS	Simpson-Angus Rating Scale
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Simpson Angus Scale
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TID	thrice daily
TK	Toxicokinetic
T_{max}	time to maximum plasma concentration

Abbreviation	Definition
ULN	upper limit of normal
US	United States
VAS	visual analog scale
VLMT	Verbal Learning and Memory Test
WOCBP	women of childbearing potential

5 INTRODUCTION

5.1 Background on Schizophrenia

Schizophrenia is a long-term mental disorder involving a breakdown in the relation between thought, emotion, and behavior, and leads to faulty perception, inappropriate actions and feelings, withdrawal from reality and personal relationships into fantasy and delusion, and a sense of mental fragmentation. Symptoms include delusions, hallucination, disorganized speech or behavior, and impaired cognitive ability.[1] The prevalence of schizophrenia is between 0.6% and 1.9% in the United States population.[2] Moreover, a claims analysis has estimated that the annual prevalence of diagnosed schizophrenia in the United States (US) is 5.1 per 1000 lives.[3] It is found equally in males and females, with males usually having an earlier onset of symptoms.[4]

Antipsychotic drugs (APDs) are the mainstay of treatment for schizophrenia.[5] All currently available antipsychotics act through blockage of all or subsets of dopamine receptors in the brain. First-generation APDs include chlorpromazine and haloperidol; treatment with these agents is marked by high rates of parkinsonian extrapyramidal symptoms (EPS) and tardive dyskinesia and they consequently have limited use today. The second-generation agents, that include risperidone, olanzapine, quetiapine, lurasidone, aripiprazole, and lumateperone, tend to have lower levels of EPS or tardive dyskinesia and are currently the most commonly prescribed APD class. However, the second-generation drugs also have problematic side effects that include significant weight gain, metabolic disturbances, sedation, and akathisia.[6, 7, 8] These side effects contribute to poor medication adherence resulting in frequent relapses and hospitalizations.[9, 10] Thus, there is a need for medications for schizophrenia which act through alternative mechanisms.

Central muscarinic receptors have been hypothesized to be therapeutic treatments for schizophrenia based on several converging lines of evidence including both animal and human studies.[11, 12] There are 5 subtypes of muscarinic receptors (M1-M5). The therapeutic effect of central muscarinic receptor agonism is thought to be due to agonism of M1 and M4 receptors in the central nervous system (CNS).[13] However, compounds that agonize M1 and M4 receptors are often not specific enough not to also agonize M2 and M3 receptors outside of the CNS due to the highly conserved allosteric binding sites that the receptors share, leading to adverse events (AEs) related to activation of these peripheral receptors. Thus, any potential benefit of muscarinic agonists in schizophrenia (or other indications such as Alzheimer's disease [AD]) has been outweighed by the occurrence of AEs associated with peripheral cholinergic side effects (nausea, vomiting, diarrhea, sweating, and excess salivation).

5.2 Background on KarXT (Xanomeline Tartrate and Trospium Chloride)

Xanomeline tartrate is a muscarinic-cholinergic receptor agonist. It has agonistic activity at all 5 muscarinic receptors, but preferentially stimulates M_1 and M_4 receptors and binding to M_1 and

M_4 receptors in the CNS, which is thought to be responsible for the drug's potential therapeutic effects (Roth, unpublished data). A recent study reports that xanomeline is a very potent M_4 muscarinic agonist in vivo, measured by various second messenger assays.[14] Xanomeline also enters the brain rapidly achieving a brain to plasma ratio of greater than 10 making it an attractive CNS drug candidate.[15]

Xanomeline does not have any direct binding activity on dopaminergic receptors, suggesting that its mechanism of action is unrelated to direct dopamine involvement.

Previous double-blind, placebo-controlled clinical trials have provided strong evidence that xanomeline has clinically relevant antipsychotic efficacy. In a multicenter outpatient trial in AD (N = 343), 3 doses of xanomeline (up to 225 mg/day) and placebo were assessed for 26 weeks.[16, 17] Significant dose-dependent improvements in psychotic symptoms relative to placebo were observed. Moreover, psychotic symptoms resolved quite rapidly in subjects who were symptomatic at baseline and a dose-dependent reduction in the emergence of psychotic symptoms versus placebo was also observed. In a completer analysis, cognitive improvement was also found suggesting longer treatment intervals may be necessary for cognitive enhancement.[16, 17] In a subsequent small (N = 20) double-blind, placebo-controlled inpatient trial in treatment-resistant subjects with schizophrenia, xanomeline (225 mg/day) demonstrated robust and relatively rapid improvement in psychosis compared to placebo. In addition, improvement in both negative symptoms and cognitive impairment was observed.[18]

In both the AD and schizophrenia trials, as well as in previous healthy volunteer studies, dose-dependent "cholinergic" AEs were also reported, namely vomiting, nausea, diarrhea, sweating, and hypersalivation. These side effects were frequent and, at the higher doses of xanomeline, led to significant rates of discontinuation in the AD studies. This "cholinergic" AE profile curtailed further development of xanomeline as a single agent.

It is believed that the procholinergic AEs associated with xanomeline are mediated by xanomeline's stimulation of *peripheral* rather than *central* muscarinic receptors, which would make these AEs theoretically amenable to counteracting peripheral anticholinergic treatment. Trospium chloride is a peripherally acting muscarinic antagonist which binds to and antagonizes all 5 muscarinic receptor subtypes.[19] It is a commonly used generic drug approved for over 10 years by the US Food and Drug Administration (FDA) and by European authorities to treat overactive bladder and is generally well tolerated.[19] Several human subject studies have demonstrated that trospium does not appreciably cross the blood-brain barrier, consistent with the drug's quaternary ammonium structure.[20]

KarXT is a novel combination of xanomeline tartrate and trospium chloride. Karuna hypothesized that the addition of trospium would mitigate peripheral procholinergic side effects (vomiting, nausea, diarrhea, sweating, and hyper-salivation) and thus provide a strategy to allow xanomeline to be administered and stimulate brain muscarinic receptors with a decreased side effect burden. Phase 1 studies in healthy volunteers of this combination demonstrated that KarXT reduced these side effects by 46% compared to xanomeline alone.[21] Moreover, the

remaining cholinergic AEs were generally mild to moderate in severity and transient in nature, often lasting a few hours without recurrence and were generally single-episode. In general, KarXT was well tolerated in healthy adult volunteers. These encouraging safety data prompted further work to assess KarXT for the treatment of schizophrenia and potentially other CNS disorders.

Karuna has recently completed an adequate and well-controlled, randomized, multi-center Phase 2, placebo-controlled, inpatient clinical trial of acute psychosis with schizophrenia in 182 adult subjects (KAR-004). KarXT demonstrated a statistically significant and clinically meaningful 11.6 point mean reduction in total Positive and Negative Syndrome Scale (PANSS) at 5 weeks compared to placebo ($p < 0.0001$), with statistical separation at each time point assessed (2, 4 and 5 weeks), and also demonstrated good overall safety and tolerability.

The purpose of the current study is to evaluate the long-term safety and tolerability of KarXT (xanomeline 125 mg/trospium 30 mg) administered twice daily (BID) in adult outpatients with Diagnostic and Statistical Manual–Fifth Edition (DSM-5) diagnosis of schizophrenia.

Xanomeline is currently not approved or marketed in any country. Trospium is marketed in the US and other regions of the world for the treatment of overactive bladder.

5.2.1 Nonclinical Studies

The following is a summary of the important nonclinical safety and toxicology studies. More detailed information can be found in the KarXT Investigator's Brochure (IB).

The acute toxicity of xanomeline tartrate was evaluated in mice and rats. All animals were observed for 2 weeks for mortality and clinical signs of intolerance, and then necropsied for gross examinations. In-life findings attributed to the test article included excessive muscarinic-mediated pharmacology, such as excessive salivation, hypoactivity, ataxia, soft stools, exophthalmos, ocular discharge, tremors, and convulsions, with survivors typically appearing normal by Day 3 or Day 4. Gross findings at necropsy were generally unremarkable (eg, gas-distended or mucous-filled gastrointestinal [GI] tracts after oral dosing).

KarXT-301 was a 14-day, repeat dose study of KarXT in rats where relatively high doses of xanomeline and trospium were given, with either xanomeline alone or in combination with trospium. Seven groups of 10 rats/sex/group were administered either vehicle (reverse osmosis water), xanomeline alone at 37, 75, 150, or 300 mg/kg/day (split into BID doses, every 12 hours), or xanomeline/trospium combination doses of 150/200 mg/kg/day or 225/400 mg/kg/day, respectively (split into BID doses, every 12 hours).

Satellite animals were included for the collection of plasma after the first and last doses for the determination of drug concentrations of each parent drug in support of toxicokinetic (TK) assessments.

There was no target-organ toxicity revealed by clinical pathology or by gross or microscopic assessments. All intolerance could be attributed to recognized pharmacology of either test article.

No dose-related ophthalmic observations were noted. Findings were not indicative of specific target organ toxicity. In short, no new hazard was identified.

Clinical observations noted in most animals administered 300 mg/kg/day xanomeline included hypoactivity, clear oral discharge, dilated pupils, irregular or labored respiration, and rough haircoat, among other observations. These findings are generally consistent with the anticipated pharmacology of xanomeline.

Three TK animals in the low-dose combination group died or were euthanized in extremis. It is unclear to what extent the combination treatment effects versus the different handling of these animals (including 3 plasma samplings per animal) contributed to these deaths. If gavage accidents were involved (as happened with some TK animals), then they were not detected at gross necropsy. There was no microscopic evidence of toxicity seen in any toxicity animals in this group or in the higher-dose combination group.

Three toxicology and 3 TK animal deaths (total of 6) occurred in the high-dose combination group. Two toxicology animals had evidence of gavage accidents. For the third, the cause of death was undetermined, and a test article-related effect cannot be ruled out, but esophageal muscular degeneration/regeneration is indicated in some dosing-related trauma. If gavage accidents were involved, then they were not detected at gross necropsy. There was no evidence of target organ microscopic findings in GI tract or any other tissue of any animal, including the early death toxicity animals.

A pharmacodynamics (PD)-mediated reduction in GI motility is consistent with the anti-muscarinic effects of trospium on intestinal musculature. Fecal retention, malabsorption, cessation of eating, dehydration, and rapid deterioration followed with continued dosing. Cessation of dosing in the high-dose combination animals that survived led to rapid recovery, implying the deleterious effects had been PD-related. No effects on food consumption were seen in any xanomeline-alone group. The lack of microscopic findings in the GI tract of any early death or surviving animal implies that the adverse effects were pharmacologically mediated rather than direct target organ toxicity.

Twenty-eight Day Repeat-Dose Studies with Xanomeline in Rats and Monkeys: Rats were fed xanomeline tartrate at 0, 0.05, 0.1, or 0.2% daily and monkeys were fed xanomeline tartrate daily at 0, 5, 12.5, or 30 mg/kg. All animals survived until necropsy. Safety findings in rats included reduced body weight in the high-dose group, increases in gamma-glutamyl-transferase, cholesterol, and bilirubin, slight decreases in triglycerides, bile duct hyperplasia, higher serum potassium (males), and lower serum globulin (females). Findings in monkeys were dose-related and included signs of intolerance such as emesis, salivation, diarrhea, hypoactivity, weight loss, and treatment-related tachycardia in the high-dose animals.

Forty-Day Repeat Dose Study of KarXT in Rats (KarXT-302): Six groups of 15 rats/sex/group were given vehicle, xanomeline alone at 75 or 150 mg/kg/day, trospium alone at 100 mg/kg/day, or xanomeline/trospium combination at doses of 75/50 mg/kg/day or 150/100 mg/kg/day, with

all doses split into BID doses. Satellite rats (TK animals) were included for collection of plasma after the first and last doses to determine concentrations of each drug. Dosing was initially planned to be 90 days, but was terminated after 40 days because of unexpected deaths in the TK animals. No target organ toxicity was seen. Safety findings included pharmacologically mediated constipation in the trospium alone and combination groups, and mild biliary hyperplasia in the high-dose xanomeline-alone and combination groups. There were 4 unscheduled deaths in TK animals; 2 in the high-dose xanomeline-alone group (150 g/kg/day) and 2 in the high-dose combination group (150 mg/kg/day xanomeline plus 100 mg/kg/day trospium). Both xanomeline-only animals had necropsy gross findings of a gavage accident and cause of death could not be determined. All toxicology animals survived to their scheduled sacrifice. The Sponsor considers that the volume depletion and trauma of multiple bleeds (3 per animal) followed by reduced absorption of fluids and nutrients secondary to reduced GI motility with continued BID dosing, explains the greater demise of TK animals relative to toxicity animals.

Based on the results of the 90-day rat toxicology study, oral administration of trospium chloride and xanomeline tartrate alone or in combination to Crl:CD(SD) rats BID (12 hours ±60 minutes apart) at dosage levels of 25 and 50 mg/kg/dose trospium chloride, 37 and 75 mg/kg/dose xanomeline tartrate and a combination of 37/25, 75/25, and 75/50 mg/kg/dose xanomeline tartrate/trospium chloride for a minimum of 90 days resulted in minimal to moderate bile duct hyperplasia in the livers of the xanomeline tartrate and combination (xanomeline tartrate and trospium chloride) group males.

Although there were no notable differences in the incidence of bile duct hyperplasia when comparing the single vs combination groups, there was an increased severity observed in the combination group males (specifically the 75/25 and 75/50 mg/kg/dose combination group males) when compared to the xanomeline tartrate group males at the terminal euthanasia. The bile duct hyperplasia was considered adverse in the high-dose xanomeline tartrate group males and in the 75/25 and 75/50 mg/kg/dose combination group males due to instances of moderate severity. Therefore, the no-observed-adverse-effect level was considered to be 50 mg/kg/dose for trospium chloride, 37 mg/kg/dose for xanomeline tartrate, and 37/25 mg/kg/dose for the combination of xanomeline tartrate/trospium chloride. At these doses for males, mean plasma AUC_{0-24} values were 27,700 pg•hr/mL for trospium, 146,000 pg•hr/mL for xanomeline, and 4510 + 111,000 pg•hr/mL for trospium + xanomeline, respectively, on Day 91.

At these doses for females, mean plasma AUC_{0-24} values were 9230 pg•hr/mL for trospium, 267,000 pg•hr/mL for xanomeline, and 16,700 + 171,000 pg•hr/mL for trospium + xanomeline, respectively, on Day 91. The absence of bile duct hyperplasia in females cannot be explained from differences in drug exposure. At the recovery euthanasia, bile duct hyperplasia was still present, but was limited to minimal severity and there was a decreased incidence in both the xanomeline tartrate and combination group males. There was also no notable difference in severity between the single vs combination groups at the recovery euthanasia. Given the decreased incidence/severity, in combination with the improved histologic appearance of bile

ducts at the recovery euthanasia (ie, smaller/flattened epithelium, non-inflammatory, and an absence of portal bridging), changes at the recovery euthanasia were consistent with a partial resolution of bile duct hyperplasia. With an absence of correlating serum liver enzyme elevations, bile acid alterations or hepatocellular degeneration, necrosis or regeneration, and with the apparent reversibility following cessation of treatment, these findings appear to have been tolerable by the affected animals. Therefore, the maximum tolerated dose was considered to be 50 mg/kg/dose for trospium chloride, 75 mg/kg/dose for xanomeline tartrate, and 75/50 mg/kg/dose for the combination of xanomeline tartrate/trospium chloride.

For males, corresponding mean plasma AUC_{0-24} values were 27,700 pg•hr/mL for trospium, 822,000 pg•hr/mL for xanomeline, and 133,000 + 276,000 pg•hr/mL for trospium + xanomeline, respectively, on Day 91. For females, corresponding mean plasma AUC_{0-24} values were 9230 pg•hr/mL for trospium, 2,090,000 pg•hr/mL for xanomeline, and 17,600 + 950,000 pg•hr/mL for trospium + xanomeline, respectively, on Day 91.

In summary, no new "combination" findings were discovered; toxicology studies revealed the familiar exaggerations of systemic and CNS muscarinic effects that had previously been seen with xanomeline or trospium at high doses. Target organ findings with xanomeline alone were limited to biliary hyperplasia in the 28-day rat study but not the 28-day or 12-month monkey study, though similar findings were described in a 6-month monkey study. With KarXT, biliary hyperplasia was not observed in the 14-day rat study but was reported in the 40-day rat study. Notably, these hyperplastic findings are not thought to represent pre-neoplastic lesions, because they were of low severity; no fibrosis or associated hepatocellular changes, and no significant effects were seen on hepatobiliary-related serum chemistry.

5.2.2 Completed Clinical Studies

Refer to the IB for complete information regarding previous clinical studies conducted with xanomeline by Eli Lilly, and studies KAR-001, KAR-002, KAR-003 and KAR-004 conducted by Karuna Therapeutics using xanomeline with trospium.

To date, more than 840 subjects or volunteers have been exposed to xanomeline tartrate (oral formulation, either alone, in combination with trospium, or as the combination drug KarXT) in 19 completed clinical studies conducted either by Eli Lilly or Karuna Therapeutics, some for as long as 3 years. In those studies, significant improvements in cognition and reduced psychotic symptoms were observed.

A study of xanomeline monotherapy in subjects with schizophrenia was reported in 2008.[18] In this pilot study, the effects of xanomeline were examined in 20 schizophrenia subjects utilizing a double-blind, placebo-controlled, 4-week study design. Subjects treated with xanomeline did significantly better than subjects in the placebo group on Brief Psychiatric Rating Scale total scores and PANSS total scores (ie, 24-point change over placebo, $p = 0.04$). In the cognitive test battery, subjects in the xanomeline group showed improvements relative to placebo in some of the cognitive domains of verbal learning and short-term memory function. These studies

demonstrated the potential for xanomeline as a treatment for psychosis and cognition across multiple subject populations.

Study H2Q-EW-E001, conducted by Eli Lilly, had 36 male healthy volunteers in 4 groups of 9, who were administered escalating single doses of xanomeline tartrate in increments of 1, 5, 10, 25, 50, 75, 100 and 150 mg. Each group took 2 ascending doses of xanomeline tartrate and 1 dose of placebo in a single subject blind manner. There were no serious AEs (SAEs). Adverse events included watery diarrhea, nausea, dizziness, sweating, shivering, mild disorientation, increased blood pressure (BP), increase(s) in sitting and standing heart rate, slight increase in supine systolic BP, and postural hypotension.

The clinical experience with KarXT initiated by Karuna Therapeutics to date includes 3 completed Phase 1, clinical pharmacology studies in healthy volunteers (KAR-001, KAR-002, and KAR-003) and one completed Phase 2 study (KAR-004) in adult inpatients with DSM-5 schizophrenia.

The first study conducted by Karuna, KAR-001 was a Phase 1, double-blind, randomized, multiple-dose, pilot study comparing xanomeline administered alone to xanomeline administered in combination with trospium chloride in normal healthy volunteers. This study consisted of 2 arms, in which xanomeline was administered three times daily (TID), alone, at a total daily dose of 225 mg in 1 arm, and the second arm received the same dose of xanomeline in combination with trospium chloride 20 mg administered BID, a total daily dose of 40 mg. Subjects were treated for 7 days. The goal was to determine whether this dosing regimen would reduce the cholinergic side effects of xanomeline by co-administration of the muscarinic antagonist, trospium.

Overall, treatment with xanomeline 225 mg daily + trospium 40 mg daily administered over 7 days was considered safe and well tolerated. The results of key and supportive endpoints showed a numerical reduction (although not statistically significant) in visual analog scale (VAS) scores for cholinergic events for the xanomeline + trospium treatment arm compared to the xanomeline-alone treatment arm. Specifically, consistent numerical reduction in VAS scores for the xanomeline + trospium treatment arm was observed for the supportive endpoints of maximum weekly individual VAS scores and mean daily maximum composite VAS scores.

Results of the clinician-administered scales were supportive of a reduction in vomiting, feelings of nausea, excess salivation, and sweating that interfered with daily activities in the xanomeline + trospium treatment arm compared to the xanomeline-alone treatment arm.

There were no meaningful differences between treatment groups in heart rate, resting BP, orthostatic BP or any electrocardiogram (ECG) parameters including QT. A small subset of subjects in both treatment arms had transient increases in heart rate and orthostatic BP changes which may have contributed to syncope and postural dizziness in those subjects. Two subjects (both in the xanomeline-alone arm) experienced syncope. The incidence of orthostatic AEs in the KarXT group was approximately one-half that of subjects in the xanomeline-alone group.

The most commonly reported treatment-emergent AEs (TEAEs) in KAR-001 (≥20% of subjects in either treatment arm) were hyperhidrosis, salivary hypersecretion, nausea, dizziness postural, and diarrhea. Subject incidences of these 5 TEAEs was higher in the xanomeline-alone treatment arm (61.8%) compared to the xanomeline + trospium treatment arm (34.3%).

Overall, treatment with xanomeline 225 mg combined with trospium chloride 40 mg administered over 7 days was considered safe and well tolerated. The observed side effect profile was consistent with the known safety profile of xanomeline and trospium chloride. The incidence of TEAEs and cholinergic TEAEs was lower in the xanomeline + trospium treatment arm compared to the xanomeline-alone treatment arm.

Study KAR-002 was a Phase 1, double-blind, randomized, multiple-dose adaptive design pilot study to evaluate the safety and tolerability of KarXT in normal healthy volunteers. Subjects received either 100 mg xanomeline + 20 mg trospium BID or placebo. The first cohort of this study was stopped after 1.5 days when the FDA put the program on hold due to a preliminary rat finding in the 14-day study. This study used a new formulation of KarXT in which xanomeline and trospium were combined into a single dose form and given BID. Safety findings included an increase in orthostatic complaints. Caution should be used in drawing conclusions from this study, as subjects did not have time to reach steady state plasma levels from dosing, as only 3 doses were given.

Study KAR-003 was a Phase 1, double-blind, randomized, multiple-dose, adaptive design, inpatient pilot study to evaluate the safety and tolerability of KarXT in normal healthy volunteers. The primary objective of this study was to assess the safety and tolerability of 7 days of daily administration of KarXT at various dose combinations, administered BID. Subjects received either KarXT or placebo (3:1 ratio). All subjects on KarXT received 2 days of 50 mg xanomeline + 20 mg trospium BID, and then increased to different doses for Days 3 to 7. This study also used the new formulation of KarXT in which xanomeline and trospium were combined into a single dosage form and given BID.

There was a relatively high degree of variability in xanomeline and trospium exposures between individuals in all cohorts, which is consistent with previous results with KarXT, xanomeline-alone, and trospium-alone. Peak plasma concentrations were observed at a median time of 2.0 hours for xanomeline and 1.0 hour for trospium across all treatment groups and study days.

Although there was insufficient data to draw a definitive conclusion regarding the impact of trospium on the pharmacokinetics (PK) and bioavailability of xanomeline, or the impact of xanomeline on the pharmacokinetics and bioavailability of trospium, the PK results suggest that neither drug had a meaningful impact on the PK behavior of the other drug.

During the 2-day lead-in phase, the most common AEs (≥20% of subjects) when all the subjects completed dosing were dry mouth, nausea, and constipation. For the treatment groups that completed dosing, although the incidence of TEAEs was lower in the KarXT 100/20 BID

(66.7%) group compared to KarXT 125/40 group (88.9%), the incidence of cholinergic TEAEs (nausea, vomiting, diarrhea, sweating, and excess salivation) was similar between the 2 groups. The most commonly reported TEAEs (≥20% of subjects in either treatment group) in these groups were dizziness, nausea, dry mouth, headache, vomiting, dyspepsia, somnolence, vision blurred, and dysuria. For the treatment groups that did not complete dosing (KarXT 150/20 BID group and KarXT 150/40 BID group), the cholinergic TEAEs were generally higher compared to the treatment groups that completed dosing.

Overall, anticholinergic TEAEs appeared to occur primarily in the treatment groups that were dosed with 40 mg trospium BID (KarXT 150/40 BID and KarXT 125/40 BID groups), particularly when paired with 125 mg xanomeline BID, suggesting to consider slightly lowering the trospium dose from 40 mg BID in future studies. All TEAEs were mild or moderate in severity, and there were no SAEs or deaths. Treatment-emergent AEs were primarily cholinergic or orthostatic (and a few anticholinergic). Doses of 100 mg and 125 mg BID of xanomeline were well tolerated when paired with 20 mg and 40 mg BID of trospium, respectively. The safety and tolerability profile of KarXT 100/20 BID and KarXT 125/40 BID was acceptable and supports further evaluation at similar doses in future studies. Doses of KarXT 150/20 BID and 150/40 BID were not well tolerated in this study. A pairing of 150 mg xanomeline with 40 mg trospium appeared to be better tolerated than 150/20, but some subjects still experienced tolerability issues.

Study KAR-004 was a Phase 2 randomized, double-blinded study to assess the safety, tolerability, and efficacy of KarXT in adults with DSM-5 schizophrenia, hospitalized with acute psychosis. The primary objective of the study was to assess the efficacy of KarXT (125/30 BID) versus placebo in reducing PANSS total scores in adult inpatients with a DSM-5 diagnosis of schizophrenia. Subjects received either KarXT or placebo (1:1 ratio) for a treatment period of 5 weeks. All subjects on KarXT received a lead-in dose of KarXT 50/20 BID for the first 2 days followed by KarXT 100/20 BID on Days 3 to 7. On Day 8, dosing was titrated upwards to KarXT 125/30 BID unless the subject was continuing to experience AEs from a previous dose increase of 100/20 BID.

A total of 182 subjects were enrolled and randomized (92 placebo; 90 KarXT). Of these subjects, 170 (87 [94.6%] placebo; 83 [92.2%] KarXT) received at least one dose of study drug and had at least one post-baseline PANSS assessment (Modified Intent to Treat population used for the efficacy analyses). Discontinuation rates were similar between the 2 treatment groups; 37 subjects discontinued the study early (19 [20.7%] placebo; 18 [20.0%] KarXT). The most common reason for early discontinuation was consent withdrawn (14 [15.2%] placebo; 14 [15.6%] KarXT) followed by Adverse Event (2 [2.2%] placebo; 3 [3.3%] KarXT).

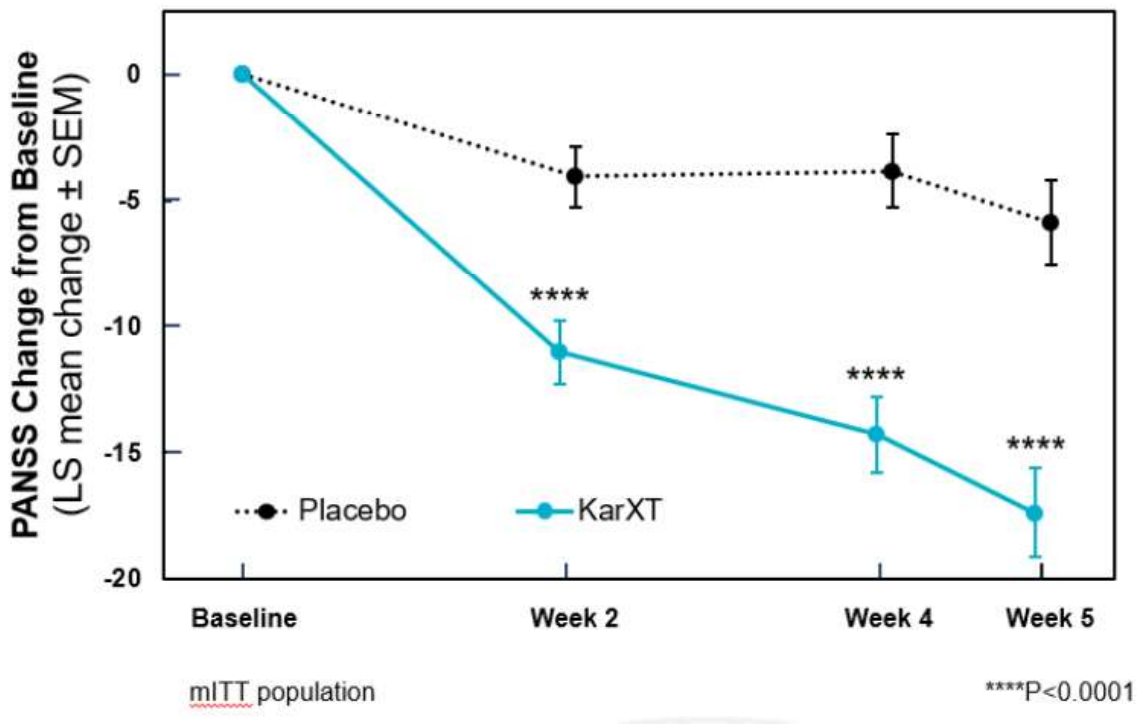
Treatment-emergent adverse events (TEAE) were reported in 43.3% of subjects in the placebo group and 53.9% of subjects in the KarXT group. The most commonly reported TEAEs were constipation, nausea, dry mouth, dyspepsia, and vomiting, and were more common (≥ 5% higher or twice that of placebo) in the KarXT group than in the placebo group.

There were 27.8% and 42.7% of subjects in the placebo and KarXT groups, respectively, who experienced at least 1 TEAE related to study drug. The most commonly reported study drug related TEAEs for the placebo and KarXT total groups were nausea, constipation, dry mouth, dyspepsia, and vomiting and were more common (≥ 5% higher or twice that of placebo) in the KarXT group than in the placebo group. The majority of the reported TEAEs were mild (27.8% placebo; 36.0% KarXT) or moderate (14.4% placebo; 16.9% KarXT) in severity. Two severe TEAEs were reported during the study. One subject in the placebo group had a severe TEAE of worsening schizophrenia symptoms, and 1 subject in the KarXT high dose group had a severe event of increased psychosis which was reported as an SAE possibly related to KarXT by the investigator. There were no other SAEs reported during the study and there were no deaths during the study.

The pattern and course of safety findings in KAR-004 were consistent with the known safety profile from earlier studies of both xanomeline monotherapy and xanomeline combined with trospium (KarXT). Even though the qualitative AE profile was consistent with earlier Phase 1 PK/safety studies in healthy volunteers, the relative tolerability burden was lower in the current study of schizophrenia patients receiving KarXT than in the healthy volunteers. In addition, the safety and tolerability of KarXT was favorable and notably free of many common side effects associated with current antipsychotic drugs.

KarXT demonstrated statistically significant and clinically meaningful reduction in total PANSS score at all time points over 5 weeks compared to placebo (Figure 1). The primary efficacy endpoint result for the study (change from baseline (CFB) in PANSS total score between the placebo group and the KarXT group at Visit 9/Week 5) showed a statistically significant decrease in PANSS total score ($p<0.0001$). The statistically significant difference in CFB between the treatment groups was there at Visit 6/Week 2 ($p<0.0001$) and continued to Visit 8/Week 4 and Visit 9/Week 5. Overall, the decrease from baseline in PANSS total score for the KarXT group was statistically significantly greater compared to the placebo group by treatment group for Visits 6, 8, and 9 ($p<0.0001$).

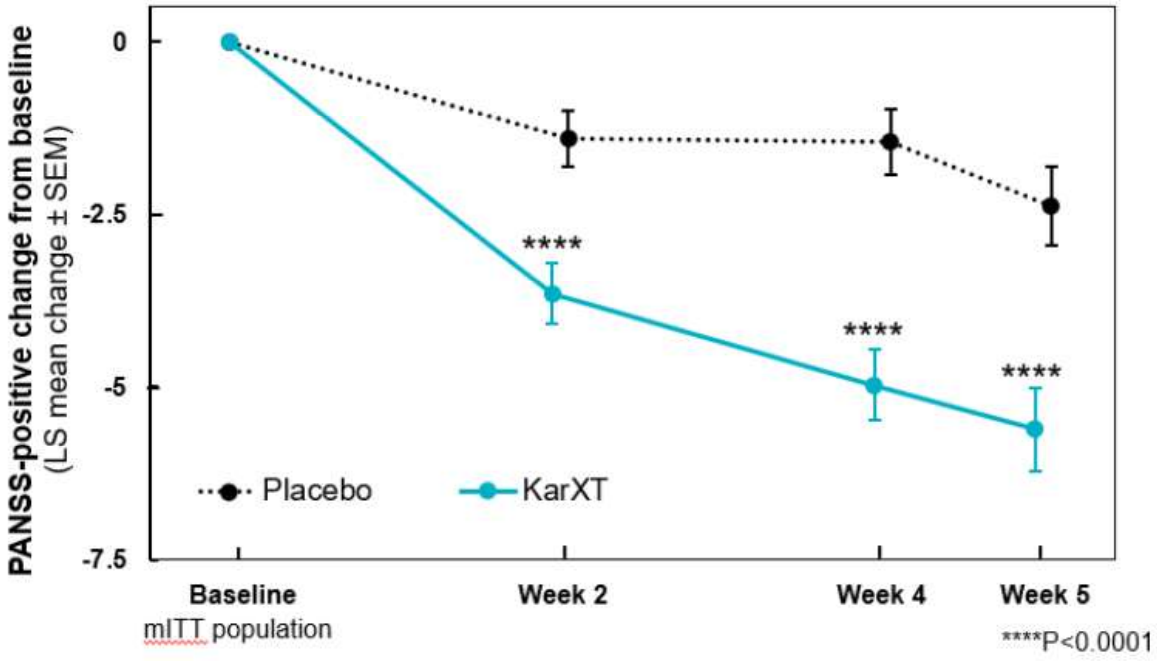
Figure 1. Change from Baseline in PANSS Total Scores (KAR-004)



1. Abbreviations: LS = least squares; mITT = modified intent-to-treat; PANSS = Positive and Negative Syndrome Scale; SEM = standard error of the mean.

A significant reduction in the secondary endpoint of PANSS-positive scores was observed ($p<0.0001$) at Week 5 as well as the 2 earlier time points (ie, Weeks 2 and 4; see Figure 2).

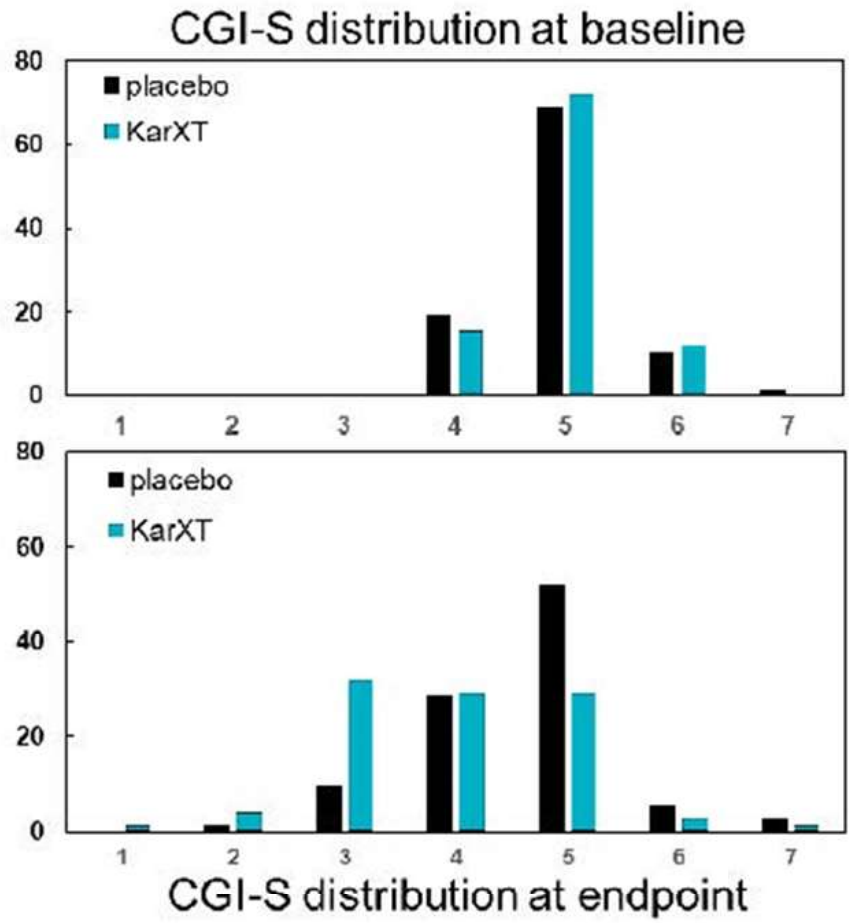
Figure 2. Change from Baseline in PANSS-Positive Scores (KAR-004)



2. Abbreviations: LS = least squares; mITT = modified intent-to-treat; PANSS = Positive and Negative Syndrome Scale; SEM = standard error of the mean.

As regards the Clinical Global Impression – Severity of Illness (CGI-S), subjects in the KarXT group overall significantly improved in ratings compared to placebo, with a p-value of <0.001 at Week 5. At Week 5, 8% of placebo subjects improved (decreased) their CGI-S ratings at least 2 levels versus 28.9% of KarXT subjects (see Figure 3).

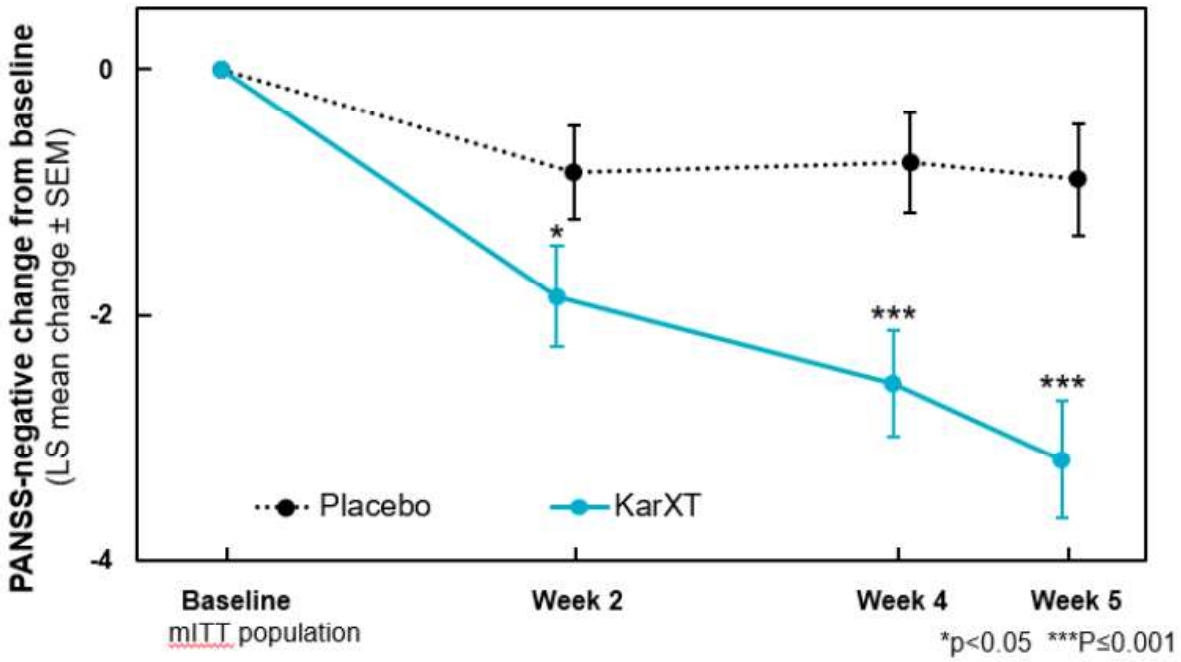
Figure 3. Change from Baseline in CGI-S (KAR-004)



3. Abbreviation: CGI-S = Clinical Global Impression–Severity.

A statistically significant reduction in the secondary endpoint of PANSS-negative score was observed ($p<0.001$) at Week 5. Overall, the changes in the KarXT group were statistically significantly greater compared to the placebo group at Visits 6, 8, and 9 ($p<0.001$). The least square mean improvement for the placebo group was 1.32 points at Week 5 (Visit 9) and the mean improvement for the KarXT group was 3.85 points leading to a mean difference of 2.53 points at Week 5 (Visit 9; see Figure 4).

Figure 4. Change from Baseline in PANSS-Negative Scores (KAR-004)



4. Abbreviations: LS = least squares; mITT = modified intent-to-treat; PANSS = Positive and Negative Syndrome Scale; SEM = standard error of the mean.

The overall safety/tolerability data were also fairly unambiguous; among the highlights:

- The overall discontinuation rate on KarXT was 20%, similar to placebo (21%). The number of discontinuations due to TEAEs was equal in the KarXT and placebo arms (N = 2 in each group)
- The dose escalation rate on KarXT was high and similar to placebo:
  - 91% of KarXT subjects escalated to 125/30 KarXT (vs 97% on placebo)
  - 4% percent de-escalated back to 100/20 KarXT dose (vs 1% on placebo)
- The overall TEAE rate on KarXT was 54% vs 43% on placebo:
  - The most common TEAEs were constipation, nausea, dry mouth, dyspepsia, and vomiting. None of these TEAEs were severe and none led to discontinuations
  - One SAE occurred in the study (the subject was on KarXT): the subject discontinued treatment and subsequently sought hospital care for worsening psychosis, meeting the regulatory definition of an SAE.
  - No syncope or mean changes in BP were seen

- A 5.5 bpm peak mean placebo adjusted resting heart rate increase with a downward trend after Week 2 was seen
- One subject (on KarXT) was discontinued due to an elevated gamma-glutamyl transpeptidase (GGT)
- There were no new safety findings associated with KarXT that have not been observed with either xanomeline alone or trospium alone in previous trials

- KarXT did not show evidence of many of the kinds of AEs that often occur in currently available antipsychotics for the treatment of schizophrenia
- The rates of the following AEs were similar for KarXT and placebo: somnolence, weight gain, and EPS
- Overall, the KAR-004 results confirm and extend the antipsychotic benefit of xanomeline observed in past studies of xanomeline alone and the well tolerated nature of KarXT. KAR-004 results support the continued development of KarXT into Phase 3 trials.

Two randomized, double-blind, placebo-controlled Phase 3 trials (KAR-007 and KAR-009) are planned in which the subjects will be exposed to either KarXT or placebo (1:1) for a period of up to 5 weeks. Subjects who complete either of these 2 studies will be eligible to roll over into this long-term open-label study.

5.3 Clinical Risks/Benefits of KarXT and Study Rationale

The risks and benefits of KarXT in humans are not fully known. KarXT is a fixed dose combination of xanomeline and trospium.

The available clinical trial data indicate that KarXT has robust efficacy and a favorable safety profile that appears unique compared to all available APDs. Most of these clinical data were generated by subjects who were either “institutionalized” or studied in an “inpatient” hospital setting. Treatment with KarXT is not associated with weight gain, sedation, or meaningful EPS changes. In contrast, these serious side-effects pose a significant risk with other APD treatments for schizophrenia and can lead to discontinuation of treatment and significant morbidity. A Phase 2 registration quality pivotal trial in 182 subjects met the primary endpoint with the PANSS total score showing a 11.6 point mean improvement compared to placebo with a highly significant ($p < 0.0001$) separation from placebo (-17.4 KarXT vs. -5.9 placebo) at Week 5. KarXT, as compared to placebo, demonstrated highly significant reduction in PANSS total scores ($p < 0.0001$) at all post randomization time points (Weeks 2, 4 and, 5) with a calculated effects size (Cohen’s d) of 0.75. KarXT, as compared to placebo, demonstrated significant improvement at all post randomization time points for PANSS positive symptom subscores, PANSS negative symptom subscores, PANSS Marder Factor negative symptom subscores, and CGI-S scores.

Over 840 subjects or volunteers have been exposed to xanomeline tartrate (oral formulation; either alone, in combination with trospium, or as the combination drug KarXT) in clinical studies. These early clinical studies, as well as nonclinical pharmacology and toxicology studies, have not revealed any specific contraindications to the use of xanomeline. The most common side effects/symptoms are the cholinergic related effects: nausea, vomiting, excess salivation, excess sweating, and diarrhea. In addition, subjects treated with xanomeline alone have reported both syncope and orthostatic dizziness. The addition of trospium decreases the peripheral cholinergic effect of xanomeline creating a better tolerated therapy. In addition, a titration phase also increases the tolerability of KarXT.

Trospium chloride has been marketed in the US for 12 years. The most frequently reported AEs reported in pivotal trials were dry mouth, constipation, abdominal pain, headache, urinary retention, and abnormal vision and accommodation. For additional information, the package insert for trospium chloride tablets for oral use can be found in the IB.

In a Phase 2 (KAR-004) clinical study, KarXT (100/20 and 125/30) significantly reduced the symptoms of schizophrenia in subjects with acute psychosis after treatment for 28 days. KarXT also showed an acceptable safety profile with the most common TEAEs being constipation, nausea, dry mouth, dyspepsia, and vomiting. All the reported TEAEs were mild or moderate in intensity. One SAE (psychotic disorder) was reported by a single subject and no deaths were reported in the study. KarXT was generally well-tolerated and found to be safe in this patient population.

KarXT represents a novel approach to the treatment of patients with schizophrenia that will provide an important and meaningful alternative to current therapies. The current tolerability and AE profile and the efficacy of KarXT justify further development of KarXT in this patient population by advancing to Phase 3 trials. Two such Phase 3 trials (KAR-007 and KAR-009) are planned where the subjects will receive the study drug (KarXT or placebo) for 5 weeks.

In the current study, regardless of treatment assignment in the preceding Phase 3 study (KAR-007 or KAR-009), all subjects will receive KarXT for a period of approximately 52 weeks with the primary objective of assessing the long-term safety and tolerability profile of KarXT in an out-patient setting. All subjects will start with a lead-in dose of KarXT 50/20 BID for Days 1 to 2 and then the dose will be titrated to 100/20 BID for Days 3 to 7, allowing the subject to adjust to KarXT before receiving a higher dose of 125/30 BID starting on Visit 3 (Day 8), unless the subject is continuing to experience AEs from the previous dose increase of KarXT 100/20 BID. All subjects who are increased to KarXT 125/30 BID, depending on tolerability, will have the option to return to KarXT 100/20 BID. Re-escalation to 125/30 BID or re-titration in cases where subject has been off KarXT for a longer period of time (at least a week) is allowed and will require a discussion between the principal investigator (PI) and the medical monitor.

Dosing will occur every 12 ±4.5 hours each day, during waking hours. KarXT should be dosed on an empty stomach (ie, at least 1 hour before a meal or 2 to 3 hours after a meal).

The current study is designed to demonstrate that long-term treatment with KarXT in adult schizophrenia subjects is safe and tolerable.

6 STUDY OBJECTIVES AND ENDPOINTS

6.1 Study Objectives

6.1.1 Primary Objective

The primary objective of the study is to assess the long-term safety and tolerability of KarXT in subjects with a DSM-5 diagnosis of schizophrenia.

6.1.2 Secondary Objectives

The secondary objective of this study is to assess the long-term efficacy and evaluate plasma concentrations of xanomeline and trospium after administration of KarXT in adults with a DSM-5 diagnosis of schizophrenia:

- To evaluate the reduction in PANSS total score
- To evaluate the reduction of PANSS positive score
- To evaluate the improvement in Clinical Global Impression Severity (CGI-S) results
- To evaluate the reduction of PANSS negative score
- To evaluate the reduction of PANSS Marder Factor negative symptoms score

6.1.3 Exploratory Objectives

The exploratory objectives of this study are:

- To evaluate cognition with the Cambridge Neuropsychological Test Automated Battery (CANTAB)
- To evaluate prolactin levels after administration of KarXT
- To characterize outcomes obtained from digital biomarkers, ecological momentary assessment administered patient reported outcomes (EMA PRO), and an EMA administered verbal learning and memory test (EMA VLMT) in schizophrenia (US only)

6.2 Study Endpoints

6.2.1 Primary Safety Endpoint

The primary safety endpoint of this study is the incidence of treatment-emergent AEs (TEAE).

6.2.2 Secondary Endpoints

6.2.2.1 Safety Endpoints

The secondary safety endpoints of this study are:

- Incidence of serious TEAEs
- Incidence of TEAEs leading to withdrawal

6.2.2.2 Efficacy Endpoints

The secondary efficacy endpoints of this study are:

- Change from baseline in PANSS total score at Week 52
- Change from baseline in PANSS positive score at Week 52
- Change from baseline in PANSS negative score at Week 52
- Change from baseline in PANSS Negative Marder Factor score at Week 52
- Change from baseline in CGI-S score at Week 52
- Percentage of PANSS responders (a ≥30% reduction in PANSS total score) at Week 52

6.2.3 Other Endpoints

6.2.3.1 Safety Endpoints

- Spontaneously reported adverse events of special interest (AESIs)
- Spontaneously reported procholinergic and anticholinergic symptoms
- Change from baseline in Simpson-Angus Rating Scale (SAS)
- Change from baseline in Barnes Rating Scale for Akathisia (BARS)
- Change from baseline in Abnormal Involuntary Movement Scale (AIMS)
- Change from baseline in body weight, body mass index (BMI), waist circumference
- Change from baseline in orthostatic vital signs (supine and standing after 2 minutes): BP (systolic and diastolic) and heart rate
- Change from baseline in clinical laboratory assessments (hematology, clinical chemistry, coagulation, urinalysis, and drug screen)
- Change from baseline in 12-lead ECG
- Change from baseline in physical examination
- Suicidal ideation scale with the use of Columbia-Suicide Severity Rating Scale (C-SSRS)

6.2.3.2 Pharmacokinetic Endpoint

- Comparison of the plasma concentrations of xanomeline and trospium measured in this study to the plasma concentrations predicted by a population pharmacokinetic (PK) model of studies KAR-007 and KAR-009

6.2.3.3 Exploratory Endpoints

The exploratory endpoints of this study are:

- Change from baseline in cognition measuring core domains of impairment in schizophrenia using CANTAB
- Change from baseline in prolactin levels
- Observed digital biomarkers of schizophrenia (US only)

- Observed ecological momentary assessment administered patient reported outcomes (EMA PRO) in schizophrenia (US only)
- Observed cognitive insight using an EMA administered verbal learning and memory test (EMA VLMT) in schizophrenia (US only)

7 INVESTIGATIONAL PLAN

7.1 Description of Overall Study Design and Plan

This is a Phase 3 multicenter, 53-week, outpatient, open-label extension (OLE) study to evaluate the long-term safety, tolerability, and efficacy of KarXT in subjects with DSM-5 schizophrenia who previously completed the treatment period of one of the two Phase 3 double-blind studies, KAR-007 or KAR-009. The study consists of a 52-week OLE treatment phase and a 7-day (±3 days) follow-up/end-of-study (EOS) visit after the last KarXT dose for subjects who complete the treatment phase and those who prematurely discontinue from the study.

After written informed consent, subjects who have completed either the KAR-007 or KAR-009 Phase 3 acute study and received the last dose of the study drug in that trial will be rolled over into the current OLE study. The assessments performed on Visit 10 (Day 35) of studies KAR-007 or KAR-009 will be considered as baseline assessments along with any additional procedures that will be performed on Day 0 of the current study. Any scheduled Day 0 assessments that were not completed on Day 35 of the acute study (KAR-007 or KAR-009) must be completed on Day 0 of the current study.

It is preferable that Baseline/Day 0 procedures of the current study be completed on the same day as Day 35 of the acute study after all Visit 10 (Day 35) procedures of the prior study KAR-007 or KAR-009 have been completed. However, with medical monitor approval, an extension of up to 3 days can be granted to complete Baseline/Day 0 procedures. This extension cannot be completed inpatient.

With medical monitor approval, participants may be permitted to complete the first 3 days (Visit 1/Day 1 to Visit 2/Day 3) of KAR-008 on the inpatient unit.

Subjects who did not complete the full treatment period, or who early terminated studies KAR-007 or KAR-009, will not be eligible to enroll in this long-term extension study.

Approximately 350 subjects are planned to be enrolled in this study (aged 18 to 65 years at time of enrollment into the preceding acute study) across approximately 30 study sites in the United States and 10 study sites in Ukraine.

In this OLE study, all subjects will receive KarXT for up to 52 weeks. Regardless of treatment assignment in the preceding Phase 3 acute study (KAR-007 or KAR-009), all subjects will start on a lead-in dose of KarXT 50/20 BID for the first 2 days (Days 1 and 2), followed by KarXT 100/20 BID for the remainder of Week 1 (Days 3 to 7). On Visit 3 (Day 8), dosing will be titrated upwards to KarXT 125/30 BID unless the subject is continuing to experience AEs from the previous dose of KarXT 100/20 BID. All subjects who are increased to KarXT 125/30 BID, depending on tolerability, will have the option to return to KarXT 100/20 BID for the remainder of the treatment period. Re-escalation to 125/30 BID or re-titration in cases in which the subject has been off KarXT for a longer period of time (at least a week) is allowed and will require a discussion between the PI and the medical monitor. Additional changes to KarXT

dosing (e.g., temporary dose reductions) may be permitted as clinically indicated upon approval by the medical monitor.

Beginning after Visit 9/Day 84, interim visits will be completed with flexibility between in-clinic visits, approximately once every 4 weeks. Whenever possible, interim visits should be conducted by telemedicine; however, sites will have the option to schedule on-site interim visits, and are encouraged to use additional unscheduled as necessary, to facilitate subject retention and ensure adherence to study objectives. .

All subjects will have questionnaires administered throughout the study (see Schedule of Assessments Table 2). Analyses of change from baseline in diagnostic measures will be performed.

Safety will be assessed through spontaneous AEs including AESIs, procholinergic and anticholinergic symptoms; SAEs and AEs leading to discontinuation of KarXT; SAS; BARS; AIMS; body weight; BMI; waist circumference; orthostatic vital signs; clinical laboratory assessments (hematology, clinical chemistry, coagulation, urinalysis, and drug screen), 12-lead ECG; physical examination; and C-SSRS will be evaluated throughout the study as scheduled. Section 11 provides complete details on these safety assessments.

Efficacy will be assessed through PANSS total score, PANSS-positive score, PANSS-negative score, PANSS Negative Marder Factor score, and CGI-S score at scheduled visits. Refer to Section 12 for more details.

Plasma concentrations of xanomeline and trospium will be evaluated. Details are provided in Section 13.

Exploratory assessments include cognition testing using CANTAB; prolactin levels; digital biomarkers of schizophrenia (US Only); Ecological Momentary Assessment (EMA) Patient Reported Outcomes (PRO; US Only) and EMA Verbal Learning and Memory Test (VLMT; US Only). Smartphone-based assessments (i.e., digital biomarkers of schizophrenia, EMA PRO, EMA VLMT and AiCure technology) will be optional. Exploratory assessments will be evaluated during scheduled visits or on specified study days. See Section 14 for more details.

A safety follow-up/end of study (EOS) visit (Visit 30/Day 371) will be performed for all subjects after the last dose of KarXT for subjects who complete the treatment phase and those who prematurely discontinue from the study.

An Independent Safety Monitoring Committee (ISMC) will be responsible for periodically reviewing the safety data from this study and confirming that the study may continue.

Table 1 presents the Study Drug Dosing Scheme.

Table 1. Study Drug Dosing Scheme

Period:	Open-Label Extension Treatment[a]						EOT/ET	EOS/UNS
Day:	Day 1	Day 3 +1 day	Day 8[b] ±1 day	Day 14 ±2 days	Days 28-70 ±3 days	Days 84-350 ±3 days	Day 364 ±3 days	Day 371 ±3 days
Visit:	Visit 1	Visit 2	Visit 3 [b]	Visit 4	Visits 5-8	Visits 9[c] -28	Visit 29	Visit 30
Xanomeline/ trospium chloride (KarXT)*:	50/20 BID	100/20 BID	125/30 BID (Option: 100/20 BID)[d]	125/30 BID (Option: 100/20 BID)[d,e]	125/30 BID (Option: 100/20 BID)[d,e]	125/30 BID (Option: 100/20 BID)[d,e]	125/30 BID (Option: 100/20 BID) [d,e]	N/A
Comment(s):	2-day lead-in dose	Upward titration of dose	Upward titration of dose					7 (±3) days after completion of the EOT or ET visit

Abbreviations: BID = twice daily; EOS = end of study; EOT = end of treatment; ET = early termination; N/A = not applicable; PI = principal investigator; UNS = unscheduled.

* All the KarXT doses are in mg xanomeline/mg trospium.

a. At Visit 1 (Day 1) subjects will initiate dosing with KarXT BID. Visits 2, 3, 4, 5, 6, 7, 8, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, and 30 are in-clinic/on-site visits. Visits 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28 are interim visits and can be conducted via telemedicine or on-site.
b. Subject to receive at least 8 doses of KarXT 100/20 prior to escalating to the KarXT 125/30 dose.
c. Beginning after Visit 9/Day 84, interim visits will be completed with flexibility between in-clinic visits, approximately once every 4 weeks.
d. All subjects who are increased to KarXT 125/30, depending on tolerability, will have the option to return to KarXT 100/20 BID.
e. Re-escalation to 125/30 BID or re-titration in cases where subject has been off KarXT for a longer period of time (at least a week) is allowed and will require a discussion between the PI and the medical monitor. Additional changes to KarXT dosing (e.g., temporary dose reductions) may be permitted as clinically indicated upon approval by the medical monitor.

7.2 Discussion of Study Design

The KarXT clinical development program includes this open-label extension study to evaluate the long-term safety, tolerability, and efficacy of KarXT in subjects with schizophrenia who participated in either of the 2 Phase 3 double-blind clinical studies and completed the treatment period.

This study will allow subjects that were randomized into a preceding Phase 3 study (KAR-007 or KAR-009) to reinstitute (or initiate treatment if a placebo subject) KarXT therapy. Subjects will receive KarXT (with the same lead-in dose of KarXT 50/20 BID), regardless of treatment assignment from the preceding Phase 3 study. Thus, subjects who received placebo during the preceding Phase 3 study who may not have demonstrated clinical benefit, nonetheless, may be considered appropriate for the current study, as all subjects will receive KarXT.

The dosing plan for this study has been established and follows the earlier studies. All eligible subjects will receive the same lead-in doses of KarXT (KarXT 50/20 BID). Dosing will be titrated to 100/20 BID on Day 3 and further titrated to 125/30 BID on Visit 3 (Day 8), unless the subject continues to experience AE(s) from the previous dose increase of KarXT.

During the study, all subjects who are increased to the highest dose of KarXT, depending on tolerability, will have the option to return to the next lower dose of KarXT (100/20 BID). Re-escalation to 125/30 BID or re-titration in cases where subject has been off KarXT for a longer period of time (at least a week) is allowed and will require a discussion between the PI and the medical monitor.

Beginning after Visit 9/Day 84, interim visits will be completed with flexibility between in-clinic visits, approximately once every 4 weeks thereafter. Whenever possible, interim visits should be conducted by telemedicine; however, sites will have the option to schedule on-site interim visits, and are encouraged to use additional unscheduled visits as necessary to facilitate subject retention and ensure adherence to study objectives.

A 52-week treatment phase is considered to be sufficient to demonstrate the long-term safety and tolerability of KarXT. A sample size of approximately 350 subjects is also determined to be an appropriate number of evaluable subjects to assess the long-term safety of KarXT administration. Section 5.2 details the nonclinical and clinical background information available on KarXT, including dose rationale.

7.3 End of Study

A subject will have fulfilled the requirements for study completion if/when the subject has completed the study treatment, including the EOS visit or the last scheduled visit as indicated in the Schedule of Assessments (Table 2) in accordance with the protocol.

7.4 Independent Safety Monitoring Committee

For the purpose of this study, the ISMC is an independent group of individuals with pertinent expertise that reviews on a regular basis accumulating safety and tolerability data from the clinical study. The ISMC will include 3 clinicians and a reporting statistician. This committee will be responsible, on a periodic basis, for confirming the safety and tolerability of KarXT throughout the study, with particular focus on assessing for any new or long-term toxicities that might be involved with KarXT.

The reviews will allow a comparison of event rates and detection of safety signals, and to identify important safety information. The ISMC charter will contain the details of the types of data to be reviewed, the defined triggers for review, the minimum frequency of meetings (timed, if no triggers), and the communication plan for disseminating review recommendations.

8 SELECTION OF STUDY POPULATION

Section 7.1 provides information regarding the number of subjects planned to be enrolled.

8.1 Inclusion Criteria

Individuals must meet all of the following criteria to be included in the study:

1. Subject is aged 18 to 65 years, at time of enrollment into the preceding acute study (KAR-007 or KAR-009).
2. Subject is capable of providing informed consent.
    a. A signed informed consent form must be provided before any study assessments are performed.
    b. Subject must be fluent in (oral and written) English (United States only) or local language (Ukraine only) to consent.
3. Subject has completed the treatment period on study drug (through Day 35 -2 days) of Studies KAR-007 or KAR-009.
4. Subject resides in a stable living situation, in the opinion of the investigator.
5. Subject has an identified, reliable informant/caregiver willing to be able to address some questions related to certain study visits, if needed. An informant/caregiver may not be necessary if the subject has been the patient of the investigator for ≥1 year.
6. Women of childbearing potential (WOCBP) or men whose sexual partners are WOCBP must be willing and able to adhere to the contraception guidelines as defined in Section 8.4.1 and Appendix 1.

8.2 Exclusion Criteria

Subjects will be excluded from the study if 1 or more of the following criteria is/are applicable:

1. Risk for suicidal behavior during the study as determined by the investigator's clinical assessment and C-SSRS as confirmed by the following:
    a. Subject answers "Yes" to "suicidal ideation" Item 4 (active suicidal ideation with some intent to act, without specific plan) or Item 5 (active suicidal ideation with specific plan and intent) on the C-SSRS assessment.
    b. Nonsuicidal self-injurious behavior is not exclusionary.
2. Any clinically significant abnormality including any finding(s) from the physical examination, vital signs, ECG, or laboratory test at the end-of-treatment visit of studies KAR-007 or KAR-009 that the investigator, in consultation with the medical monitor, would consider to jeopardize the safety of the subject.
3. Female subject is pregnant, breast feeding or planning to become pregnant during the course of the study.

4. If, in the opinion of the investigator (and/or Sponsor), subject is unsuitable for enrollment in the study or subject has any finding that, in the view of the investigator (and/or Sponsor), may compromise the safety of the subject or affect his/her ability to adhere to the protocol visit schedule or fulfill visit requirements.
5. Subjects with extreme concerns relating to global pandemics such as coronavirus disease 2019 (COVID-19) that preclude study participation.
6. Risk of violent or destructive behavior.
7. Subjects participating in another investigational drug or device trial or planning on participating in another clinical trial during the course of the study.

8.3 Safety Laboratory Evaluations for Eligibility

Subjects may be enrolled into KAR-008 prior to receipt of the results from the safety laboratory evaluations collected on Visit 10 of the preceding acute study. These subjects will be dosed on Day 1 of KAR-008; however, subjects may be withdrawn from KAR-008 depending upon the clinical significance of the results of the Visit 10 safety laboratory evaluations at the discretion of the PI in consultation with the medical monitor. Abnormal lab values deemed clinically significant must be recorded as AEs. Subjects with elevated liver function tests (LFTs) per the DILI criteria must be withdrawn from further participation in KAR-008. Retesting of labs is allowed once, with the exception of elevated LFTs.

8.4 Study Withdrawal, Removal, and Replacement of Subjects

If a subject discontinues study treatment and is withdrawn from the study for any reason, the study site must immediately notify the medical monitor. The date and the reason for study discontinuation must be recorded on the electronic case report form (eCRF). Subjects who complete or discontinue early from the study will be asked to return to the study site within 7 (±3) days of the EOT or ET visit to complete EOS assessments as indicated in the Schedule of Assessments (Table 2).

In the event that a subject discontinues prematurely from the study because of a treatment emergent AE (TEAE) or serious TEAE, the TEAE or serious TEAE will be followed up until it resolves (returns to normal or baseline values) or stabilizes, or until it is judged by the investigator to no longer be clinically significant.

Once a subject is withdrawn from the study, the subject may not re-enter the study.

A subject may voluntarily withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following:

- progressive disease
- unacceptable toxicity or AE

- subject withdrawal of consent: at any time, a subject's participation in the study may be terminated at his/her request or on the basis of the investigator's clinical judgment; the reason for subject withdrawal will be noted on the eCRF
- intercurrent illness: a condition, injury, or disease unrelated to the primary diagnosis that became apparent during treatment and necessitated the subject's termination from the study
- general or specific changes in the subject's condition that renders them ineligible for further treatment according to the inclusion/exclusion criteria (eg, subject has need for a medication prohibited by the protocol)
- subject fails to adhere to the protocol requirements (eg, drug noncompliance [if a subject is off KarXT for >7 consecutive days])
- violation of entry criteria, ie, enrolled subjects who are later discovered not to meet eligibility criteria
- development of suicidal or assaultive behavior
- alcohol abuse or illegal drug use
- pregnancy, as indicated in Section 11.8
- Sponsor's decision to discontinue study

Subjects who withdraw from the study will be encouraged to complete the same final evaluations as subjects completing the study according to this protocol, particularly safety evaluations. The aim is to record data in the same way as for subjects who completed the study.

Reasonable efforts will be made to contact subjects who are lost to follow-up. A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study center. These efforts must be documented in the subject's file. Subjects with AEs ongoing at end of study will be followed until the AE is resolved or the subject is considered to be in stable condition.

The Sponsor has the right to terminate the study at any time in case of SAEs or if special circumstances concerning the KarXT become known, making further treatment of subjects impossible. In this event, the investigator(s) will be informed of the reason for study termination.

8.4.1 Pregnancy

No evidence of mutagenicity, or treatment effects on reproduction, fertility, or fetal parameters have been demonstrated in animals following administration of xanomeline, but there are no adequate and well-controlled studies in pregnant women (FDA Pregnancy Category B). Animal reproduction studies of trospium chloride have shown an adverse effect on the fetus, but potential benefits may warrant the use of the drug in pregnant women despite the risk (FDA Pregnancy Category C).

Therefore, WOCBP in this study must be willing to use a highly effective method of birth control (see Appendix 1 for a list of acceptable highly effective methods of contraception) during the study and for 30 days after the last dose of KarXT. WOCBP will have a urine pregnancy test on Day 0 (before receiving KarXT) and thereafter, as designated at other scheduled visits (Table 2). In case of positive urine pregnancy test result, a serum sample should be sent to the central laboratory to confirm the result. Pregnant women are excluded from this study because the effects of KarXT on the developing human fetus are unknown with the potential for teratogenic or abortifacient effects.

Because there is an unknown but potential risk for AEs in nursing infants secondary to treatment of the mother with KarXT, women who become pregnant must discontinue KarXT immediately.

The effects of KarXT on sperm are unknown. Male subjects whose sexual partners are WOCBP must agree to use a highly effective method of birth control (see Appendix 1 for a list of acceptable highly effective methods of contraception) and must not impregnate a sexual partner during or for 30 days after the last dose of KarXT. They must also agree to refrain from sperm donation for 30 days after the last dose of KarXT.

WOCBP will be instructed that known or suspected pregnancy occurring during the study should be confirmed and reported to the investigator. If a female subject becomes pregnant, the investigator must withdraw her from the study without delay. The subject must not receive any further doses of the KarXT. The investigator must notify the Sponsor or their designee of any female subject or female partner of a male subject that becomes pregnant while participating in the study. If the female subject or the female partner of the male subject is willing and able to consent to pregnancy follow-up, she will be followed until her pregnancy reaches term. Only those procedures that would not expose the pregnant female patient to undue risk will be performed. See Section 11.8 for further reporting and monitoring details.

Full details of the pregnancy will be recorded on the withdrawal page (exit form) of the eCRF, or a Pregnancy Reporting Form will be completed if the subject has completed the study. Notification of the pregnancy should be submitted via the Pregnancy Reporting Form within 24 hours of knowledge of the pregnancy. Pregnancy is not to be considered an AE; however, it must be reported using the same procedure as described for reporting SAEs, Section 11.7.4.

8.5 Completion of the Study or Lost to Follow-up

The study will be completed when all subjects have completed their study-related procedures in accordance with the protocol.

Every reasonable effort will be made to contact subjects who are lost to follow-up to obtain EOS information. Details regarding follow-up efforts are to be documented in the subject's medical records/source documentation.

8.6 Study Termination

The availability of any new adverse safety information related to KarXT may result in stopping the study. An investigator, Sponsor, or Institutional Ethics Committee (IEC)/Institutional Review Board (IRB) may take such actions. If the study is terminated for safety reasons, subjects will be notified immediately and assured that appropriate treatment and follow-up will be available. If an investigator terminates the study, the Sponsor, subjects, and IEC/IRB will be informed about the reason for such action. Similarly, if the Sponsor terminates the study, it will inform the investigators, the IEC/IRB, and the subjects of the reason for such an action. Similar notifications will be sent by the IEC/IRB if it takes such an action.

9 TREATMENTS

9.1 Details of Study Treatments

KarXT is formulated as hard hydroxypropyl methylcellulose oral capsules containing 2 distinct populations of drug beads, 1 of which is loaded with xanomeline tartrate and the other of which is loaded with trospium chloride. Each capsule contains the free base equivalent of xanomeline and trospium according to the desired dosage strength. In addition to the active ingredients, the drug beads contain microcrystalline cellulose (MCC). The beads are not coated and are formulated for immediate release of the active ingredients.

9.1.1 Identity of Study Treatments

Active study agents for treatment group will be size 0, Swedish orange, opaque, and hydroxypropyl methylcellulose hard capsules. For the 2-day lead-in period (Days 1 and 2), subjects will receive capsule strength KarXT 50/20 BID, followed by 2 capsules of KarXT 50/10 mg BID or a dosage of 100/20 mg BID for a total daily dose of 200/40 mg for the remainder of Week 1 (Days 3 to 7). At the beginning of Visit 3 (Day 8), dosing may be increased to 2 capsules of KarXT 62.5/15 mg or a dosage of 125/30 mg BID for a total daily dose of 250/60 mg, depending on tolerability. Investigators have the option to return a subject to KarXT 100/20 mg BID. Re-escalation to 125/30 BID or re-titration in cases where subject has been off KarXT for a longer period of time (at least a week) is allowed and will require a discussion between the PI and the medical monitor.

Additional changes to KarXT dosing (e.g., temporary dose reductions) may be permitted as clinically indicated upon approval by the medical monitor (see also Section 9.4).

KarXT 50/10 mg is composed of 44.4% xanomeline tartrate, 5.8% trospium chloride, excipients 37.59% MCC, 11.5% lactose monohydrate, 0.3% ascorbic acid and 0.5% talc in a size 0, Swedish orange, hydroxypropyl methylcellulose hard capsule.

KarXT 50/20 mg is composed of 33.4% xanomeline tartrate, 8.7% trospium chloride, excipients 39.8% MCC, 17.3% lactose monohydrate, 0.3% ascorbic acid and 0.5% talc in a size 0, Swedish orange, hydroxypropyl methylcellulose hard capsule.

KarXT 62.5/15 mg is composed of 41.7% xanomeline tartrate, 6.5% trospium chloride, excipients 38.1% MCC, 12.9% lactose monohydrate, 0.3% ascorbic acid and 0.5% talc in a size 0, Swedish orange, hydroxypropyl methylcellulose hard capsule.

All investigational agents are to be stored according to requirements as specified on the Investigational Product label.

9.1.2 Packaging and Labeling

The study packaging and labeling will be performed by Corealis Pharma, located in Laval, Quebec, Canada and Catalent Pharma Solutions, located in Winchester, Kentucky (labelling for

the US sites), and Catalent Pharma Solutions, located in Philadelphia, Pennsylvania (labelling for Ukrainian sites). All packaging and labeling operations will be performed according to Good Manufacturing Practice for Medicinal Products and the relevant regulatory requirements.

Bulk supply bottles are labeled with the name of the drug, recommended storage conditions, the name and address of the manufacturer and the Investigational Use Statement (for the US sites: "Caution: New Drug – Limited by Federal [USA] Law to Investigational Use" and for the Ukrainian sites: "For clinical trial use only" or similar wording).

Further details on labeling of investigational product will be provided in the Pharmacy Manual.

9.1.3 KarXT Storage

Prior to dispensing KarXT to the subjects, it must be stored at controlled room temperature 15˚C-25˚C.

9.1.4 KarXT Retention

KarXT must be retained until completion or termination of the study, and written authorization from the Sponsor has been received. All unused and used KarXT must be destroyed at the site or returned, as specified by Sponsor. It is the investigator's responsibility to ensure that the Sponsor has provided written authorization prior to return or destruction, and that appropriate records of the disposal are documented and maintained. No used or unused KarXT may be disposed until fully accounted for by the study monitor.

9.2 Dosage Schedule

Subjects who roll over into KAR-008 will start dosing with KarXT on Day 1 of the current study. Baseline/Day 0 procedures must be completed prior to Day 1 and preferably on the same day as Visit 10 (Day 35) of the preceding acute study KAR-007 or KAR-009. The assessments performed on Visit 10 (Day 35) of studies KAR-007 or KAR-009 will be considered as baseline assessments along with any additional procedures that must be performed up to Day 1 of the current study.

The first dose of the KarXT will be self-administered in the morning of Day 1 and the last dose will be self-administered in the morning of EOT Visit (Day 364). KarXT should be administered daily BID on an empty stomach (ie, at least 1 hour before a meal or 2 to 3 hours after a meal). Some considerations for dosing and PK blood withdrawals are provided in the subsections below. As described in Section 10.2, subjects may opt to utilize AiCure Technology to monitor KarXT dosing adherence.

9.2.1 Day 0

- The site pharmacist will prefill 2 child resistant pill bottles with sufficient quantities of 50mg/20mg of KarXT for the first 2 days of dosing and a sufficient quantity of

50mg/10mg pills to accommodate subsequent BID dosing of KarXT at 100/20 level until Visit 3/Day 8.

- Sites will send the subject home with instruction to begin self-administration of KarXT BID in the morning of Day 1.
- For all KarXT doses, the first dose is to be self-administered in the morning and the evening dose will be self-administered at 12 (±4.5) hours after the morning dose.
- Remind the subject to bring their pill bottles to the next clinic visit.

9.2.2 Visit 1/Day 1 Dosing

- Initiate BID dosing with KarXT 50/20.
- All subjects must have taken 4 doses of the KarXT 50/20 before dose escalation to KarXT 100/20 BID. Subjects should be instructed to contact the investigator in the event they did not take all 4 doses of KarXT 50/20 prior to Visit 2/Day 3.

9.2.3 Visit 2/Day 3 Dosing

Initiate BID dosing with KarXT 100/20. Subjects who have not taken their morning dose of 50/20 KarXT at the time of the study visit should receive their first dose of KarXT 100/20 at the time of the study visit.

Subjects who plan to utilize AiCure to track adherence must have completed AiCure training and registration prior to dosing.

- All the subjects must have taken at least 8 doses of the KarXT 100/20 before dose escalation to KarXT 125/30 BID. Subjects should be instructed to contact the investigator in the event they did not take at least 8 doses of KarXT 100/20 prior to Visit 3/Day 8.
- Remind the subject to bring their pill bottles to the next clinic visit.

9.2.4 Visit 3/Day 8

- If dose escalation to the KarXT 125/30 level is confirmed by investigator order, the site pharmacist will prefill 1 child resistant bottle with a sufficient quantity of 62.5 mg/15 mg pills to accommodate BID dosing of KarXT at 125/30 level until the next clinic visit.
- If the subject has not yet taken their morning dose of 100/20 KarXT at the time of the study visit, the subject should receive their first dose of KarXT 125/30 at the time of the study visit.
- A single PK sample should be drawn at Visit 3/Day 8, and the dose of KarXT and time of most recent dosing should be recorded. Whenever possible, the PK sample should be obtained within 1 to 2 hours of dosing.
- Remind the subject to bring their pill bottle to the next clinic visit.

In the event that the subject is not escalated to KarXT 125/30, in accordance with investigator order, dispense sufficient quantities of 50 mg/10 mg pills to continue BID dosing of KarXT at the 100/20 level until next clinic visit.

9.2.5 Visit 4/Day 14 Dosing and PK Considerations

- If dose of KarXT 125/30 BID was confirmed by investigator order, the site pharmacist will prefill 1 child resistant bottle with a sufficient quantity of 62.5 mg/15mg pills to accommodate BID dosing of KarXT at 125/30 level until the next clinic visit.
- A single PK sample should be drawn at Visit 4/Day 14, and the dose of KarXT and time of most recent dosing should be recorded.
- Remind the subject to bring their pill bottle to the next clinic visit.

If dose of KarXT 100/20 BID was confirmed by investigator order, dispense sufficient quantities of 50 mg/10 mg pills to continue BID dosing of KarXT at the 100/20 level until next clinic visit.

9.2.6 Visits 5 to 8 (Days 28 to 70) Dosing

- If dose of KarXT 125/30 BID was confirmed by investigator order, the site pharmacist will prefill 1 child resistant bottle with a sufficient quantity of 62.5 mg/15 mg pills to accommodate BID dosing of KarXT at the 125/30 level until the next clinic visit.
- Remind the subject to bring their pill bottle to the next clinic visit.

If dose of KarXT 100/20 BID was confirmed by investigator order, dispense sufficient quantities of 50 mg/10 mg pills to continue BID dosing of KarXT at the 100/20 level until next clinic visit.

9.2.7 Visits 9 to 29 (Days 84 to 364) Dosing

- If dose of KarXT 125/30 BID was confirmed by investigator order, the site pharmacist will prefill two child resistant bottles with a sufficient quantity of 62.5 mg/15 mg pills to accommodate BID dosing of KarXT at the 125/30 level until the next clinic visit.
- For Days 84, 168, and 280, a single PK sample will be collected and the dose of KarXT and time of most recent dosing should be recorded.
- See Section 9.4.1 for management of KarXT dose changes and PK sampling.
- Remind the subject to bring their pill bottles to the next clinic visit.

If dose of KarXT 100/20 BID was confirmed by investigator order, dispense sufficient quantities of 50 mg/10 mg pills to continue BID dosing of KarXT at the 100/20 level until next clinic visit.

9.3 Measures to Minimize Bias: Study Treatment Assignment

9.3.1 Method of Study Treatment Assignment

The 9-digit Subject Number previously assigned to the subject in the study KAR-007/KAR-009 will continue to be used in the current study KAR-008. This number will be associated with the subject throughout the current study.

9.3.2 Blinding

This is an open-label study; therefore, blinding is not applicable.

9.4 Dosage Modification

Subjects will self-administer the KarXT as described in Section 7.1 and in accordance with the Schedule of Assessments (Table 2). The KarXT doses were selected based on the previous preclinical and clinical studies (see Section 5.2). Per the protocol, subjects will be evaluated for dose adjustments starting at Visit 3 through the remainder of the treatment period (see Section 9.2).

Additional changes to KarXT dosing (e.g., temporary dose reductions) may be permitted as clinically indicated upon approval by the medical monitor.

9.4.1 Extended Dosing Interruptions and Re-titration

Re-escalation to 125/30 BID or re-titration in cases where subject has been off the KarXT for a longer period of time (at least a week) is allowed and will require a discussion between the principal investigator (PI) and the medical monitor.

All subjects approved by the PI and medical monitor will resume KarXT by repeating the lead-in dosing scheme used at the start of study. Subjects will start with a lead-in dose of KarXT 50/20 BID for the first 2 days after restarting study drug. Then the dose will be titrated to 100/20 BID for at least the next 4 days, allowing the subject to adjust to KarXT before receiving a higher dose of 125/30 BID after restarting study drug, unless the subject is continuing to experience AEs from the previous dose, in which case the subject will remain on KarXT 100/20 BID.

9.5 Treatment Accountability and Compliance

The pharmacist or other designated individual will maintain records of study treatment delivered to the study site, the inventory at the study site, the distribution to each subject, and the return of materials to the Sponsor or designee for storage or disposal. These records should include dates, quantities, batch/serial numbers, expiration dates, temperature log, and unique code numbers assigned to the product and study subjects.

Administration of KarXT will be supervised by study site personnel (during in-clinic visits). The pharmacist (or designee) will be responsible for dispensing KarXT into labeled child-resistant

pill bottles for subjects use when at home. The quantity of KarXT capsules dispensed should be sufficient to cover the period (including visit window) until next planned study visit. Please refer to the Schedule of Assessments in Section 10 and the study Pharmacy Manual for details.

Investigators will maintain records that adequately document that the subjects were provided with the correct study treatment supply and reconcile the usage of the study drug. Investigational product will not be returned to the Sponsor or designee or destroyed until accountability has been fully monitored through the end of the study. KarXT accountability will be assessed periodically by the assigned study monitor.

9.6 Prior and Concomitant Therapy

9.6.1 Prior and Concomitant Medications

Concomitant medications ongoing as of Visit 10/Day 35 of the preceding acute study (KAR-007 or KAR-009) will be captured in the eCRF as baseline therapy. Thereafter, all medications and other treatments taken by the subject during the study, including those treatments initiated before the start of the study drug administration, must be recorded on the KAR-008 eCRF.

Restricted prior therapies are provided below.

During the study (ie, from the time of enrollment at baseline visit [Day 0] until study completion (EOS), subjects should refrain from the use of any new concomitant medications without the prior approval of the investigator. The administration of any other concomitant medications during the study period is prohibited without the prior approval of the investigator unless its use is deemed necessary in a medical emergency. Any medication or therapy that is taken by or administered to the subject during the course of the study must be recorded in the eCRF. The entry must include the dose, regimen, route, indication, and dates of use.

All the subjects enrolled into the study must not take the below mentioned prohibited medications for the duration of the treatment period.

- Oral or long-acting injectable antipsychotic medications, monoamine oxidase inhibitors, mood stabilizers (ie, lithium), anticonvulsants (eg, lamotrigine, Depakote), tricyclic antidepressants (eg, imipramine, desipramine), selective serotonin reuptake inhibitors, or any other psychoactive medications except for anxiolytics that were taken on an as needed basis (eg, lorazepam, chloral hydrate).

Note: Please direct questions relating to prohibited medications to the medical monitor.

9.6.2 Concomitant Medications for Anxiety and/or Sleep Aid

Subjects are allowed to take benzodiazepines (up to 4 mg lorazepam/day or equivalent) for anxiety, agitation, and insomnia on a PRN basis. Subjects may also use non-benzodiazepine medications (eg, zolpidem, zaleplon) as a sleep aid, also on a PRN basis. Study sites must record the use of such medications in the eCRF and subject's source document.

Note: Cognition testing should not be done within 8 hours of receiving a benzodiazepine or sleep medication.

10 STUDY PROCEDURES

Table 2 outlines the timing of procedures and assessments to be performed throughout the study. Section 11.6 specifies laboratory assessment samples to be obtained. See Sections 11, 12, 13, and 14 for additional details regarding efficacy, safety, PK, and exploratory assessments, respectively.

COVID-19 testing will be completed in accordance with clinical site standard operating procedures. If a subject tests positive for COVID-19 during the study, they may be quarantined as needed and any scheduled visits should be rescheduled or conducted via telemedicine per the discretion of the investigator. If the subject requires hospitalization, an SAE should be reported, and the subject should be followed up as outlined in Section 11.7.3.

Table 2. Schedule of Assessments

DAY	0	1	3 (+1d)	8 (± 1d)	14 (± 2d)	28 (± 3d)	42 (± 3d)	56 (± 3d)	70 (± 3d)	84 (± 3d)	98 (± 3d)	112 (± 3d)	126 (± 3d)	140 (± 3d)	154 (± 3d)	168 (± 3d)
WEEK		**1**			**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**
VISIT	**Baseline[1]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10[a]**	**11**	**12**	**13**	**14**	**15**
TYPE OF VISIT	Clinic		Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic
PROCEDURE																
Written informed consent	X															
Subject eligibility verification	X															
Urine pregnancy test (WOCBP only)[b]	(X)[2]			X	X	X	X	X	X	X		X		X		X
Urine drugs of abuse and alcohol testing[c]	(X)[2]		X	X	X	X	X	X	X	X		X		X		X
Review of inclusion/exclusion criteria	X															
Height, body weight, BMI, waist circumference[d]	X				X	X	X	X	X	X		X		X		X
Complete physical examination[e]	X															
Targeted physical examination[f]	(X)[2]			X	X	X	X	X	X	X		X		X		X
Spontaneous AEs[g]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review of concomitant medications[h]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs: BP and HR[i]	X		X	X	X	X	X	X	X	X		X		X		X
Resting ECG (12-lead)[j]	X				X							X				
Blood samples for clinical laboratory tests[k]	X				X	X			X			X				X
Blood sample for prolactin[l]	X				X							X				
Functional constipation inquiry[m]	X		X	X	X	X	X	X	X	X		X		X		X
Determination of dose titration				X	X											
PK blood draw[n]				X	X					X						X
PANSS[o]	X				X	X		X		X		X		X		X
C-SSRS[p]	X		X	X	X	X	X	X	X	X		X		X		X
CGI-S scale	X				X	X		X		X		X		X		X
Cognition testing[q]	X					X		X		X						X

DAY	**0**	**1**	**3 (+1d)**	**8 (± 1d)**	**14 (± 2d)**	**28 (± 3d)**	**42 (± 3d)**	**56 (± 3d)**	**70 (± 3d)**	**84 (± 3d)**	**98 (± 3d)**	**112 (± 3d)**	**126 (± 3d)**	**140 (± 3d)**	**154 (± 3d)**	**168 (± 3d)**
WEEK		**1**			**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**
VISIT	**Baseline[l]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10[a]**	**11**	**12**	**13**	**14**	**15**
TYPE OF VISIT	Clinic		Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic
PROCEDURE																
SAS	X					X						X				
BARS	X					X						X				
AIMS	X					X						X				
KarXT dispensed	X	X		X	X	X	X	X	X	X		X		X		X
Subject self-administration of KarXT		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
OPTIONAL																
AiCure registration and training[r]	X															
EMA registration and training[s]	X															
EMA PRO[t]	X				X	X		X		X		X		X		X
EMA VLMT[u]						X		X		X		X		X		X
Digital biomarkers using AiCure app[v]	X			X	X	X		X		X		X		X		X

Table 2 Schedule of Assessments (Continued from Visits 16 to 30)

DAY	182 (± 3d)	196 (± 3d)	210 (± 3d)	224 (± 3d)	238 (± 3d)	252 (± 3d)	266 (± 3d)	280 (± 3d)	294 (± 3d)	308 (± 3d)	322 (± 3d)	336 (± 3d)	350 (± 3d)	364 (± 3d)	371 (± 3d)
WEEK	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52**	**53**
VISIT	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29 (EOT/ ET)**	**30 (EOS/ UNS)[3]**
TYPE OF VISIT	Interim	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic	Clinic
PROCEDURE															
Urine pregnancy test (WOCBP only)[b]		X		X		X		X		X		X		X	X
Urine drugs of abuse and alcohol testing[c]		X		X		X		X		X		X		X	X
Height, body weight, BMI, waist circumference[d]		X		X		X		X		X		X		X	X
Complete physical examination[e]															X
Targeted physical examination[f]		X		X		X		X		X		X		X	
Spontaneous AEs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review of concomitant medications[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs: BP and HR[i]		X		X		X		X		X		X		X	X
Resting ECG (12-lead)[j]		X						X						X	
Blood samples for clinical laboratory tests[k]				X				X				X		X	
Blood sample for prolactin[l]		X						X						X	
Functional constipation inquiry[m]		X		X		X		X		X		X		X	X
PK blood draw[n]								X						X[4]	
PANSS[o]		X		X		X		X		X		X		X	X
C-SSRS[p]		X		X		X		X		X		X		X	X
CGI-S scale		X		X		X		X		X		X		X	X
Cognition testing[q]						X						X		X[4]	
SAS		X						X						X	X

DAY	182 (± 3d)	196 (± 3d)	210 (± 3d)	224 (± 3d)	238 (± 3d)	252 (± 3d)	266 (± 3d)	280 (± 3d)	294 (± 3d)	308 (± 3d)	322 (± 3d)	336 (± 3d)	350 (± 3d)	364 (± 3d)	371 (± 3d)
WEEK	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52**	**53**
VISIT	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29 (EOT/ ET)**	**30 (EOS/ UNS)[3]**
TYPE OF VISIT	Interim	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic	Interim	Clinic	Clinic
PROCEDURE															
BARS		X						X						X	X
AIMS		X						X						X	X
KarXT dispensed		X		X		X		X		X		X			
Subject self-administration of KarXT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
OPTIONAL															
AiCure adherence technology[r]															
EMA PRO[t]		X		X		X		X		X		X			
EMA VLMT[u]		X		X		X		X		X		X			
Digital biomarkers using AiCure app[v]		X		X		X		X		X		X			

Abbreviations: AE = adverse event; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; BL = baseline; BMI = body mass index; BP = blood pressure; CGI-S = Clinical Global Impression–Severity scale; C-SSRS = Columbia-Suicide Severity Rating Scale; d = day; ECG = electrocardiogram; EMAW = EMA Wellness; EOS = end of study; EOT = end of treatment; ET = early termination; HR = heart rate; PANSS = Positive and Negative Syndrome Scale; PK = pharmacokinetic; QTcF = QT interval corrected by Fridericia; SAS = Simpson-Angus Rating Scale; UNS = unscheduled visit.

1. Baseline Day 0 assessments should be rolled over from Day 35/Visit 10 of the preceding study (KAR-007 or KAR-009) whenever possible (exception: cognition which should be rolled over from Day 32). Includes pregnancy testing, complete physical exam, vital signs, ECG, safety laboratory evaluations, functional constipation inquiry, PANSS, C-SSRS, CGI-S, SAS, AIMS and BARS.
2. (X) = Optional and to be completed only if Day 0 visit does not take place on the same day of Day 35/Visit 10 of the preceding study. See footnotes for additional details.
3. Unscheduled (UNS) visits may be conducted as needed to facilitate retention and ensure adherence to study objectives. Other assessments may be performed as needed.
4. This procedure is optional and should only be performed for participants who have terminated early; PK draw is recommended if termination is due to AE.

a. Beginning after Visit 9/Day 84, and every 4 weeks thereafter, interim visits will be completed with flexibility between the in-clinic visits. Interim visits should be conducted by site staff using telemedicine (audio only, or audio + video); however, sites will have the option to schedule in-clinic visits as needed to ensure subject retention and support study objectives.
b. A urine pregnancy test for WOCBP should be performed at scheduled visits. If a urine pregnancy test is positive, a serum sample should be sent to central laboratory for confirmation of the result. A new urine pregnancy test should be performed on Day 0 visit only if subject left the inpatient unit after completion of Visit 10 of the preceding acute study but prior to completion of the Day 0 procedures of the current study.
c. A National Institute on Drug Abuse-5 (NIDA-5) urine drug screen (cannabinoids or marijuana, phencyclidine, amphetamines, opiates, and cocaine) and test for alcohol (breathalyzer or urine alcohol level) will be performed at the indicated scheduled visits. Should be performed on Day 0 visit only if subject left the inpatient unit after completion of Visit 10 of the preceding acute study but prior to completion of the Day 0 procedures of the current study.
d. Baseline height is recorded from Study KAR-007/KAR-009 Screen visit. Baseline body weight, BMI and waist circumference recorded from KAR-007/-009 Visit 10. At the indicated study visits, body weight and waist circumference will be measured and BMI calculated.
e. A complete physical examination includes body temperature (°C), general appearance, head/eyes/ears/nose/throat (HEENT), examination of thorax and, assessment of cardiac, musculoskeletal, and circulatory systems, palpations for lymphadenopathy, and limited neurological examination.
f. A targeted physical examination includes at a minimum body temperature, a check of general appearance, as well as examination of organ systems that are relevant to the investigator based on review of the subject's reported AEs, review of systems, or concomitant medication use. These also include symptom-driven physical examinations which will be performed as clinically indicated at any study visit. A targeted physical examination at Day 0 is optional, and only required if the subject has reported a new AE in the time since completing Visit 10 of the preceding acute study.
g. Adverse events as reported by subjects or observed by clinical staff. Adverse events ongoing as of Visit 10 of the preceding acute study will be recorded in the KAR-008 Medical History eCRF. Adverse events occurring after dosing with KarXT in the current study will be recorded in the KAR-008 AE eCRF. One PK blood sample may be drawn if a relevant/significant AE (based on medical judgment) is reported during a scheduled visit or if there is a dose titration or a relevant/significant AE reported during an unscheduled visit (no multiple draws). For interim visits, spontaneous AEs will be collected by telemedicine or during in-clinic visits.
h. Concomitant medications ongoing as of Visit 10/Day 35 of the preceding acute study will be captured in the eCRF as baseline therapy. Thereafter, all medications and other treatments taken by the subject during the study, including those treatments initiated before the start of the study, must be recorded on the KAR-008 eCRF. For interim visits, concomitant medications will be collected by telemedicine or during in-clinic visits.
i. Vital signs measurements should be taken at all in-clinic visits, while the subject is supine and standing after 2 minutes. BP includes systolic and diastolic BP and is to be taken in the same arm for the duration of the study. During in-clinic visits orthostatic vital signs should occur 2 (±1) hours after morning dose of KarXT whenever possible.
j. ECG should be obtained within 1 to 2 hours post morning dose whenever possible. ECG at all indicated visits should be performed before blood withdrawal for any safety laboratory tests and/or PK analysis. ECGs will be transmitted electronically to a central reader for determination of ventricular rate (bpm), PR (msec), QRS (msec), QT (msec), and QTcF (msec) measurements.
k. Refer to Section 11.6 for individual laboratory tests. For urinalysis, a urine dipstick will be performed at the site. In the event of abnormalities, the sample will be sent to the central laboratory for full microscopic urinalysis.
l. Prolactin sample is optional when using local labs.
m. Functional constipation inquiry: At specified visits, subjects will be asked whether they have experienced constipation (per the ROME III criteria and Bristol Stool Form Scale; see Appendix 2) since the last visit and if yes, whether the constipation required intervention. If the subject answers yes, sites are instructed to ask subjects to provide event date and ensure the event is documented as an AE and treatment is documented as concomitant medication.
n. PK blood samples will be collected on Days 8, 14, 84, 168, and 280. At Day 8 the PK sample should be obtained within 1 to 2 hours post dose whenever possible. In cases of dose reduction, re-escalation, re-titration, or a relevant/significant AE is reported, an additional PK sample may be collected per investigator discretion in consultation with the medical monitor.

o. It is recommended, if at all possible, that the PANSS assessment should be performed before all the other scale assessments for all visits at which it is performed.
p. The "since last visit" version should be used for C-SSRS administration. At the Unscheduled visit, the C-SSRS should be performed to monitor subjects for suicidality.
q. Cognition testing is performed using CANTAB. Cognition testing should not be done within 8 hours of receiving a benzodiazepine or sleep medication.
r. Participation in AiCure technology is optional. For subjects who opt to utilize it, AiCure should be used to self-administer KarXT beginning on Day 1 whenever possible, and no later than Visit 2, Day 3. Refer to the Study Operations Manual for details.
s. Participation in EMA is optional and is used in the US Only. See Study Operations Manual for additional details.
t. Participation in EMA PRO is optional. For subjects who opt to utilize it, EMA PRO (US Only) will be completed by the subject at home on a cellular device 3 times per day for 7 days every 28 days, beginning on Day 29. An abbreviated version of the assessment will be utilized on Days 4-6 and 15-17 to familiarize subjects with the process. Refer to Study Operational Manual for details.
u. Participation in EMA Wellness technology is optional. For subjects who opt to utilize it, cognitive insight (US Only) will be assessed using the EMA VLMT. The assessment will be completed by the subject at home on a cellular device 1 time per day for 2 days every 28 days beginning on Day 32. Refer to Study Operational Manual for details.
v. Participation in digital biomarkers using the AiCure app is optional. For subjects who opt to utilize it, digital biomarkers of schizophrenia (US Only) will be calculated through completion of a smartphone-based assessment daily by the subject for 3 days collected initially on Days 4-6, 9-11, and 15-17. Subsequently subjects will complete assessments daily for 3 days every 28 days, beginning on Day 29. Refer to Study Operational Manual for details.

10.1 Informed Consent

Informed consent forms must be approved for use by the reviewing Independent Ethics Committee (IEC)/Institutional Review Board (IRB). Before performing any study-related procedures, the investigator (or designee) will obtain written informed consent from the subject and/or caregiver (Ukraine only).

10.2 Study Procedures

Assessments and their timing are to be performed as outlined in the Schedule of Assessments (Table 2). Section 11.6 specifies laboratory assessment samples to be obtained.

Safety assessments are described in Section 11 and include spontaneous AEs including AESIs; procholinergic and anticholinergic symptoms, SAEs and AEs leading to discontinuation of the KarXT; SAS; BARS; AIMS; body weight; BMI; waist circumference; orthostatic vital signs; ECG; clinical laboratory assessments (hematology, clinical chemistry, coagulation, urinalysis, and drug screen); physical examination; and C-SSRS.

Efficacy assessments are described in Section 12 and include PANSS and CGI-S scores.

PK assessments are described in Section 13.

Exploratory assessments are described in Section 14 and include cognition testing using CANTAB; prolactin levels; digital biomarkers of schizophrenia (optional); EMA PRO (optional); and EMA VLMT (optional).

The investigator may, at his/her discretion, arrange for a subject to have an unscheduled assessment, especially in the case of AEs that require follow-up or are considered by the investigator to be possibly related to the use of KarXT. The unscheduled visit page in the eCRF must be completed. The assessments and procedures that may be performed during an unscheduled visit are outlined in the Schedule of Assessments (Table 2). Additional assessments can be performed as needed, at the discretion of the investigator, and following discussion with the medical monitor.

Study discontinuation procedures are described in Section 8.4 and Section 8.6.

10.2.1 AiCure Adherence Technology

Smartphone-based technology including AiCure will be optional for all subjects. Subjects may opt out at the beginning of the study or at any point during the treatment period. AiCure technology can be used to monitor study medication adherence in all subjects, both in the US and the Ukraine. Subjects must complete registration and training to begin utilizing AiCure technology no later than Visit 2/Day 3, prior to escalating from 50/20 to 100/20 KarXT. See Operations Manual for additional details. Additionally, the AiCure technology may be used to capture Digital Biomarker Assessment of schizophrenia symptoms of subjects in the US only.

Medication Adherence (US and Ukraine):

In subjects who opt to use smartphone-based technology, this study will employ a medication adherence monitoring platform (herein after referred to as Platform). The Platform uses artificial intelligence on smartphones to confirm medication ingestion. In addition, built-in reminders and a communication system allow real-time intervention in case of drug interruptions.

Use of this Platform will in no way supersede or replace the physician and/or prescribed medication protocol of the subjects. Because the Platform does not change the medication protocol of the subjects, but rather encourages adherence to the predefined protocol, use of this Platform presents minimal risk to the subjects. Use of the Platform will be optional for all subjects in the study.

The monitoring Platform requires that all subjects take each dose of the medication while using a smartphone. Participants will download the AiCure application on their personal smartphone device; for participants who do not have a smartphone or do not wish to use their personal smartphone but still wish to do smartphone-based assessments, site personnel will provide the participant with one of the preloaded backup provisioned devices.

When at home, study subjects will receive a medication reminder at a time within a predefined window. This notification reminds subjects to take their medication dose while using the Platform. Subjects will follow a series of prescribed steps in front of the front-facing webcam to visually confirm their ingestion of the medication. The application on the smartphone will make an automated determination of whether the subject has properly taken their medication at the prescribed time. There is no need for a healthcare provider to review the administration, nor would a healthcare provider need to be available at the time the subject takes their medication. The amount of guidance that the device provides to the subject is automatically reduced as the subject becomes more proficient at using the application.

Digital Biomarker Assessment (US only):

For subjects enrolled at US sites and who opt to use smartphone-based technology, subjects will be performing brief smartphone-based assessments using the AiCure application. Video and audio of participant behavior captured during these assessments will be used to calculate visual and auditory markers of schizophrenia symptomatology. These digital biomarkers will be used as exploratory efficacy endpoints to measure change from baseline in disease severity. See Section 14.4 for endpoint discussion. The material will be presented to subjects in one of two ways. In the first, material will be presented to subjects, and will include questionnaires provided at regular intervals during the study. Images may also be shown to subjects, and they will be asked to describe each image in a few sentences to the camera of the smartphone.

Data Collected on the AiCure Platform:

After the device confirms proper medication ingestion, video recordings will be encrypted and transmitted to a secure centralized location for further analysis, including testing for duplicate enrollment. Video and audio recordings from the Digital Biomarker assessments will be encrypted and transmitted in a similar manner. The captured data and video are reviewable

through a roles and rules restricted system ensuring privacy of the information. The system is compliant with applicable US and European data privacy laws, including General Data Protection Regulation (GDPR) (EU) 2016/679 the Health Insurance Portability and Accountability Act (HIPAA), which protects the privacy and security of healthcare information.

Phone numbers of the patients may also be collected and stored in an encrypted manner. Storing the phone numbers will allow for direct communication with patients, including automated messaging from the Platform device and contact by healthcare providers or other monitoring personnel. At no time is the phone number visible to healthcare providers or monitoring personnel. Individuals outside the clinical sites will not be provided with patient names, nor will they be given access to patient medical records.

The Platform may provide significant benefits to study subjects as well as to the other stakeholders in the trial. Subjects will benefit from rapid and tailored intervention in case of non-adherence (drug interruptions) without having to visit the clinic for unscheduled visits. Healthcare providers will have access to real-time and continuous adherence data without having to rely on self-reported data or frequent study visits by patients. Subjects who regularly fail to take their medication will be contacted by healthcare providers or other study monitoring personnel for retraining.

11 SAFETY ASSESSMENTS

Safety assessments (spontaneous AEs including AESIs; procholinergic and anticholinergic symptoms; SAEs and AEs leading to discontinuation of the KarXT; SAS; BARS; AIMS; body weight; BMI; waist circumference; orthostatic vital signs; ECG; clinical laboratory assessments [hematology, clinical chemistry, coagulation, urinalysis, and drug screen]; physical examination; and C-SSRS) will be performed at protocol-specified visits, as specified in the Schedule of Assessments (Table 2).

11.1 Demographics, Medical History, and Psychiatric History

Demographic data, and medical and psychiatric history will be recorded from the Phase 3, double-blind, acute study (KAR-007/KAR-009).

Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs on the eCRF in accordance with Section 11.7. All changes that are not present at baseline or described in the past medical history and identified as clinically noteworthy must be recorded as AEs.

11.2 Vital Signs

Orthostatic vital signs (systolic and diastolic BP and heart rate measurements) will be evaluated at all scheduled visits indicated in the Schedule of Assessments (Table 2). All vital signs will be measured supine and standing after 2 minutes. Blood pressure measurements are to be taken in the same arm for the duration of the study. During in-clinic visits, beginning with Visit 2 (Day 3), orthostatic vital signs should occur 2 (±1) hours after morning dosing, whenever possible.

Vital sign measurements will be repeated if clinically significant or machine/equipment errors occur. Out-of-range BP, or heart rate measurements will be repeated at the investigator's discretion. Any confirmed, clinically significant vital sign measurements must be recorded as AEs.

11.3 Complete/Targeted Physical Examination

A complete physical examination (body temperature, general appearance, head/eyes/ears/nose/throat [HEENT], examination of thorax and abdomen, assessment of cardiac, musculoskeletal, and circulatory systems, palpations for lymphadenopathy, and limited neurological examination) will be performed at visits as specified in Table 2. Physical examinations will be performed by a physician or qualified designee.

A targeted physical examination includes at a minimum body temperature, a check of general appearance, as well as examination of organ systems that are relevant to the investigator, based on review of the subject's reported AEs, review of systems, or concomitant medication use. These also include symptom-driven physical examinations which will be performed as clinically indicated at any study visit.

11.4 Weight, Height, Body Mass Index, and Waist Circumference

The baseline height measurement will be recorded from the lead-in Study KAR-007 or KAR-009 Screen visit. The baseline body weight, BMI and waist circumference measurements will be recorded from the KAR-007 or KAR-009 Visit 10. At the indicated visits of the current study (Table 2), body weight and waist circumference will be measured and BMI calculated. All findings should be recorded in the eCRF.

11.5 Electrocardiograms

A 12-lead, resting ECG should be obtained within 1 to 2 hours post morning dose at the visits indicated in the Schedule of Assessments (Table 2), whenever possible. ECG at all scheduled visits should be performed before blood withdrawal for any safety laboratory tests and/or PK analysis.

ECGs will be transmitted electronically to a central reader for determination of ventricular rate (bpm), PR (msec), QRS (msec), QT (msec), and QTcF (msec) measurements. An assessment of normal or abnormal will be recorded; if the ECG is considered abnormal, the abnormality will be documented on the eCRF. ECGs will be repeated if clinically significant abnormalities are observed or artifacts are present.

11.6 Laboratory Assessments

Laboratory assessment samples (Table 3) are to be obtained at designated visits as detailed in the Schedule of Assessments (Table 2).

Table 3. Laboratory Assessments

Hematology	**Serum Chemistry**	**Urine Analysis (Dipstick)**
Full and differential blood count Hct Hb MCH MCHC MCV Platelet count RBC count WBC count with differential	ALT ALP AST Albumin Uric acid BUN or urea Carbon dioxide Creatinine Creatine kinase and subtypes Electrolytes (sodium, potassium, chloride, calcium, phosphorus) GGT Glucose LDH Total bilirubin Direct bilirubin Total cholesterol HDL LDL Triglycerides Total protein	Appearance pH Protein Glucose Ketone bodies Indicators of blood and WBCs Specific gravity Urobilinogen Occult blood WBCs
HbA1c (glycated Hb test)	**Prolactin**	
Coagulation		
PT Activated PTT Fibrinogen		
Pregnancy test: A urine pregnancy test for WOCBP should be performed per the schedule of assessments (Table 2). In case of positive urine pregnancy test result, a serum sample should be sent to the central laboratory to confirm the result.		
Full and microscopic urinalysis: Chemical exam: SG, pH, bilirubin, urobilinogen, protein, glucose, ketone, hemoglobin, leukocyte esterase, nitrite, ascorbic acid Microscopic exam: RBCs, WBCs, epithelial cells, bacteria, yeasts, parasites, casts, crystals		

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; GGT = gamma-glutamyl transpeptidase; HCG = human chorionic gonadotropin; Hb = hemoglobin; Hct = hematocrit; HDL = high density lipoprotein; LDH = lactate dehydrogenase; LDL = low density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; WBC = white blood cell; WOCBP = women of childbearing potential.

Venous blood of approximately 12 to 20 mL will be withdrawn for the tests listed above at scheduled time points as per Table 2.

A minimum volume of 10 mL will be obtained to perform urinalysis (if abnormalities observed on dipstick) and urine drug screen at scheduled time points as per Table 2.

Blood and urine samples (microscopic analysis) will be analyzed at a central laboratory facility. Urine samples will first be analyzed by dipstick at the site. If the results of the dipstick indicate abnormalities to be further investigated, the sample will be sent to the central laboratory and a microscopic analysis will be performed. All laboratory reports must be reviewed, signed, and dated by the investigator. A legible copy of all reports must be filed with both the subject's eCRF and medical record (source document) for that visit. Any laboratory test result considered by the investigator to be clinically significant should be considered an AE (clinically significant AEs include those that require an intervention). Clinically significant abnormal values occurring during the study will be followed up until repeat test results return to normal, stabilize, or are no longer clinically significant.

All the study subjects will be closely monitored for the drug-induced liver toxicity (detailed in Section 11.7.5), during the study.

Other Laboratory Assessments:

- A National Institute on Drug Abuse-5 (NIDA-5) urine drug screen (cannabinoids or marijuana, phencyclidine, amphetamines, opiates, and cocaine) will be performed using a dipstick throughout the study.
- Alcohol testing will be performed using a breathalyzer or urine alcohol test.

11.7 Adverse Events

11.7.1 Adverse Events

An AE is any symptom, physical sign, syndrome, or disease that either emerges during the study or, if present at screening/baseline, worsens during the study, regardless of the suspected cause of the event. All medical and psychiatric conditions (except those related to the indication under study) present at screening/baseline will be documented in the medical history eCRF. Changes in these conditions and new symptoms, physical signs, syndromes, or diseases should be noted on the AE eCRF during the rest of the study. Clinically significant laboratory abnormalities should also be recorded as AEs. Surgical procedures that were planned before the subject enrolled in the study are not considered AEs if the conditions were known before study inclusion; the medical condition should be reported in the subject's medical history.

In accordance with the protocol, the investigator and/or study staff will elicit AEs and intercurrent illness during and at the end of the study period and these will be recorded on the appropriate page of the eCRF. Adverse events will be elicited by asking the subject a nonleading question, for example, "Have you experienced any new or changed symptoms since we last asked?" The eCRF will be completed at the end of the study as soon as the results of the final lab tests are available.

Each AE is to be documented on the eCRF with reference to date of onset, duration, frequency, severity, relationship to KarXT, action taken with KarXT, treatment of event, and outcome. Furthermore, each AE is to be classified as being serious or nonserious. Changes in AEs and resolution dates are to be documented on the eCRF.

For the purposes of this study, the period of observation for collection of AEs extends from the time of consent until the EOS or ET. Follow-up of the AE, even after the date of therapy discontinuation, is required if the AE persists until the event resolves or stabilizes at a level acceptable to the investigator.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the event should be noted. If the intensity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

The severity of AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 5.0 (Grades 1 through 5).

Specific guidelines for classifying AEs by intensity and relationship to KarXT are given in Table 4 and Table 5.

Table 4. Classification of Adverse Events by Intensity

MILD: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
MODERATE: An event that is sufficiently discomforting to interfere with normal everyday activities.
SEVERE: An event that prevents normal everyday activities.

Table 5. Classification of Adverse Events by Relationship to KarXT

UNRELATED: This category applies to those AEs that are clearly and incontrovertibly due to extraneous causes (disease, environment, etc).
UNLIKELY: This category applies to those AEs that are judged to be unrelated to the test drug but for which no extraneous cause may be found. An AE may be considered unlikely to be related to KarXT if or when it meets 2 of the following criteria: (1) it does not follow a reasonable temporal sequence from administration of the test drug; (2) it could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it does not follow a known pattern of response to the test drug; or (4) it does not reappear or worsen when the drug is readministered.
POSSIBLY: This category applies to those AEs for which a connection with the test drug administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related if or when it meets 2 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; or (3) it follows a known pattern of response to the test drug.
PROBABLY: This category applies to those AEs that the investigator feels with a high degree of certainty are related to the test drug. An AE may be considered probably related if or when it meets 3 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose (note that there are exceptions when an AE does not disappear upon discontinuation of the

drug, yet drug-relatedness clearly exists; for example, as in bone marrow depression, fixed drug eruptions, or tardive dyskinesia); or (4) it follows a known pattern of response to the test drug.

DEFINITELY: This category applies to those AEs that the investigator feels are incontrovertibly related to test drug. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose and recurs with re-exposure to drug (if rechallenge occurs); and (4) it follows a known pattern of response to the test drug.

5. Abbreviation: AE = adverse event.

11.7.2 Adverse Events of Special Interest

The AEs of special interest will be monitored and include orthostasis and liver function test elevations inclusive of drug-induced liver injury (DILI).

11.7.3 Serious Adverse Events

An SAE is any untoward medical occurrence, in the view of either the investigator or Sponsor, that:

- results in death,
- is life-threatening,
- results in inpatient hospitalization or prolongation of existing hospitalization (however, hospitalization for elective treatment of a pre-existing non-worsening condition is not considered an SAE; the details of such hospitalizations must be recorded on the medical history or physical examination page of the eCRF),
- results in persistent or significant disability/incapacity, and/or
- is a congenital anomaly/birth defect.

Other important medical events that may not be immediately life-threatening or result in death or hospitalization, based upon appropriate medical judgment, are considered SAEs if they are thought to jeopardize the subject and/or require medical or surgical intervention to prevent 1 of the outcomes defining an SAE. Serious AEs are critically important for the identification of significant safety problems; therefore, it is important to take into account both the investigator's and the Sponsor's assessment. If either the Sponsor or the investigator believes that an event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting.

11.7.4 Serious Adverse Event Reporting

An SAE occurring from the time of informed consent until EOS or ET must be reported to the Catalyst Clinical Research Pharmacovigilance group and will be communicated to the Sponsor. Any such SAE due to any cause, whether or not related to the KarXT, must be reported within **24**

hours of occurrence or when the investigator becomes aware of the event. Notification can be made using email.

Catalyst Clinical Research Pharmacovigilance email address: [redacted]

The event must be recorded on the standard AE eCRF. Preliminary reports of SAEs must be followed up by detailed descriptions later on, including clear and anonymized photocopies of hospital case reports, consultant reports, autopsy reports, and other documents when requested and applicable. SAE reports must be made whether or not the investigator considers the event to be related to the investigational drug.

Appropriate remedial measures should be taken to treat the SAE, and the response should be recorded. Clinical, laboratory, and diagnostic measures should be employed as needed in order to determine the etiology of the problem. The investigator must report all additional follow-up evaluations to the Catalyst Clinical Research Pharmacovigilance group within 24 hours of becoming aware of the additional information or as soon as is practicable. All SAEs will be followed up until the investigator and Sponsor agree the event is satisfactorily resolved.

Any SAE that is not resolved by the end of the study or upon discontinuation of the subject's participation in the study is to be followed up until it either resolves, stabilizes, returns to baseline values (if a baseline value is available), or is shown to not be attributable to the KarXT or procedures.

After EOS, any SAE that the Investigator considers related to study drug must be reported to Catalyst Clinical Safety or the Sponsor/designee.

11.7.5 Drug-Induced Liver Injury

The sponsor has incorporated the following for monitoring of drug-induced liver injuries:

- *An increase of serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) to >3 × ULN should be followed by repeat testing within 48 to 72 hours of all 4 of the usual serum measures (ALT, AST, ALP, and total bilirubin) to confirm the abnormalities and to determine if they are increasing or decreasing. An inquiry should be made about the symptoms (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, and rash).*
- *Close observation should be initiated with ALT or AST >3 × ULN:*
    - *Repeat liver enzyme and serum bilirubin tests 2 or 3 times weekly. The frequency of retesting can decrease to once per week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic.*
    - *Obtain a more detailed history of symptoms and prior or concurrent diseases.*

- *Obtain a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.*
- *Rule out acute viral hepatitis types A, B, C, D, and E, autoimmune or alcoholic hepatitis, non-alcoholic steatohepatitis, hypoxic/ischemic hepatopathy, and biliary tract disease.*
- *Obtain a history of exposure to environmental chemical agents.*
- *Obtain additional tests to evaluate liver function, as appropriate (eg, international normalized ratio, and/or direct bilirubin).*
- *Consider gastroenterology or hepatology consultations.*

- *Discontinuation of treatment should be considered if:*
  - *ALT or AST >8 × ULN*
  - *ALT or AST >5 × ULN for more than 2 weeks*
  - *ALT or AST >3 × ULN and (total bilirubin >2 × ULN or international normalized ratio >1.5)*
  - *ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (>5%)*
- *Hepatic adjudication of cases should include an evaluation for alternative causes such as viral, autoimmune, alcohol, hepatobiliary disorders, non-alcoholic steatohepatitis, concomitant medications, etc.*
- *Follow-up to resolution of elevated liver enzymes.*
- *Gamma-glutamyl transferase elevations alone should not prompt drug discontinuation.*

Subjects must be monitored closely. If close monitoring is not possible, the study drug should be discontinued.

11.7.5.1 Trial Discontinuation Criteria Other than DILI and Pregnancy

11.7.5.2 Individual Stopping Criteria

Based on NCI CTCAE v5.0, study drug will be discontinued in any subject who has a ≥ Grade 4 AE. Discontinuation or reduction in the dosage of the study drug for Grade 3 AEs other than DILI AEs (see Section 11.7.5) will be at the discretion of the investigator.

11.7.5.3 Trial Stopping Rules

The safety and tolerability aspects of KarXT will be overseen by an ISMC. The ISMC will meet periodically and review the unblinded data and will be responsible for advising the sponsor on ways to safeguard the interests of the clinical study subjects. The committee is expected to recommend sponsor whether to:

a. Continue the clinical study without modification; or
b. Continue the clinical study with modification (listing the specific modifications recommended); or
c. Terminate the study.

11.7.6 Suspected Unexpected Serious Adverse Reactions

Adverse events that meet all of the following criteria will be classified as suspected unexpected serious adverse reactions (SUSARs) and reported to the appropriate regulatory authorities in accordance with applicable regulatory requirements for expedited reporting:

- serious
- unexpected (ie, the event is not consistent with the safety information in the IB or package insert of generic trospium)
- there is at least a reasonable possibility that there is a causal relationship between the event and the study treatment

The investigator will assess whether an event is causally related to study treatment. The Sponsor (or Syneos Health) will consider the investigator's assessment and determine whether the event meets the criteria for being reportable as a 7-day or 15-day safety report. SUSARs that are fatal or life-threatening must be reported to the regulatory authorities and the IEC/IRBs (where required) within 7 days after the Sponsor (or Syneos Health) has first knowledge of them, with a follow-up report submitted within a further 8 calendar days. Other SUSARs must be reported to the relevant regulatory authorities and the IEC/IRBs within 15 calendar days after the Sponsor (or Syneos Health) first has knowledge of them.

The Sponsor (or Syneos Health) is responsible for reporting SUSARs and any other events required to be reported in an expedited manner to the regulatory authorities and for informing investigators of reportable events, in compliance with applicable regulatory requirements within specific timeframes. Investigators will notify the relevant IEC/IRBs of reportable events within the applicable timeframes.

11.7.7 Warnings and Precautions

Risk of Urinary Retention:

Trospium chloride tablets should be administered with caution to subjects with clinically significant bladder outflow obstruction because of the risk of urinary retention.

Angioedema:

Angioedema of the face, lips, tongue, and/or larynx has been reported with trospium chloride, the active ingredient in trospium chloride tablets. In one case, angioedema occurred after the first dose of trospium chloride. Angioedema associated with upper airway swelling may be life-threatening. If involvement of the tongue, hypopharynx, or larynx occurs, trospium chloride should be promptly discontinued and appropriate therapy and/or measures necessary to ensure a patent airway should be promptly provided.

Decreased Gastrointestinal Motility:

Trospium should be administered with caution to subjects with GI obstructive disorders because of the risk of gastric retention. Trospium chloride, like other antimuscarinic agents, may decrease GI motility and should be used with caution in subjects with conditions such as ulcerative colitis, intestinal atony, and myasthenia gravis.

Controlled Narrow-angle Glaucoma:

In subjects being treated for narrow-angle glaucoma, trospium chloride should only be used if the potential benefits outweigh the risks and in that circumstance only, with careful monitoring.

Central Nervous System Effects:

Trospium chloride is associated with anticholinergic CNS effects. A variety of CNS anticholinergic effects have been reported, including dizziness, confusion, hallucinations, and somnolence. Subjects should be monitored for signs of anticholinergic CNS effects, particularly after beginning treatment or increasing the dose. Advise subjects not to drive or operate heavy machinery until they know how trospium chloride affects them. If a subject experiences anticholinergic CNS effects, dose reduction or drug discontinuation should be considered.

Anticholinergic Adverse Reactions in Subjects with Moderate Renal Impairment:

Trospium is substantially excreted by the kidney. The effects of moderate renal impairment on systemic exposure are not known but systemic exposure is likely increased. Therefore, anticholinergic adverse reactions (including dry mouth, constipation, dyspepsia, urinary tract infection, and urinary retention) are expected to be greater in subjects with moderate renal impairment.

Elevation of liver enzymes:

Elevated liver enzymes have been reported in previous studies of xanomeline alone in Alzheimer's disease patients. It is notable, however, that the hepatic enzyme elevations were not observed in the Phase 1 studies in healthy volunteers and that the liver function test elevations observed in the Phase 2 schizophrenia study (KAR-004) with KarXT (a combination of xanomeline and trospium) were quite limited in contrast to the effects observed with xanomeline in the elderly Alzheimer's population. Moreover, even in the Alzheimer disease patients who experienced more hepatic enzyme elevations, the data demonstrate reversibility even with continued xanomeline treatment in those patients where there was sufficient follow-up data. Importantly, there were no Hy's law cases or elevations in total bilirubin to a value of >2X upper limit of reference range in either the xanomeline or KarXT datasets.

11.8 Pregnancy

WOCBP must have a negative pregnancy test at baseline (Day 0).

The investigator must notify the Sponsor (or designee) of any female subject or female partner of a male subject that becomes pregnant while participating in the study. Any known cases of pregnancy will be reported until the subject completes or withdraws from the study.

The pregnancy will be reported immediately by faxing/emailing a completed pregnancy report to the Sponsor (or designee) within 24 hours of knowledge of the event. The pregnancy will not be processed as an SAE; however, the investigator will follow-up with the subject until completion of the pregnancy and must assess the outcome in the shortest possible time, but not more than 30 days after completion of the pregnancy.

If a female subject becomes pregnant, the investigator must withdraw her from the study without delay. The subject must not receive any further doses of the KarXT. Upon discontinuation from the study, only those procedures that would not expose the subject to undue risk will be performed.

If the female subject or the female partner of the male subject is willing and able to consent to pregnancy follow-up, she will be followed until her pregnancy reaches term. Information regarding the pregnancy must only be submitted after obtaining written consent from the pregnant partner. The investigator will arrange counseling for the pregnant partner by a specialist to discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

The investigator should notify the Sponsor (or designee) of the pregnancy outcome by submitting a follow-up pregnancy report. If the outcome of the pregnancy involved spontaneous or therapeutic abortion (any congenital anomaly detected in an aborted fetus is to be documented), stillbirth, neonatal death, or congenital anomaly, the investigator will report the event by faxing/emailing a completed pregnancy report form to the Sponsor (or designee) within 24 hours of knowledge of the event. This event is considered as an SAE.

The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a subject is subsequently found to be pregnant after inclusion in the study, any pregnancy will be followed to term, and the status of mother and child will be reported to the Sponsor after delivery.

11.9 Overdose

The investigator must immediately notify the Sponsor of any occurrence of overdose with KarXT (total daily dose greater than 250/60 mg).

Signs and symptoms of overdose may vary considerably. They are usually manifested by increasing GI stimulation with epigastric distress, abdominal cramps, diarrhea and vomiting, excessive salivation, pallor, cold sweating, urinary urgency, blurring of vision, and eventually fasciculation and paralysis of voluntary muscles. Miosis, increases or decreases in blood pressure with or without bradycardia, and severe anxiety and panic may occur.

Supportive treatment should be used as indicated (artificial respiration, maintenance of airway, oxygen, etc.). Atropine sulfate should be available for IV or intramuscular administration.

Several doses ranging from 0.5 to 2.0 mg may be required. Epinephrine 0.1 to 1.0 mg subcutaneous may also be of value in overcoming severe cardiovascular or bronchoconstrictor responses.

Adverse events associated with overdoses should be reported on the eCRF.

11.10 Simpson-Angus Rating Scale

The SAS is an established instrument to measure drug-related extrapyramidal syndromes. It is a 10-item testing instrument used to assess gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, head dropping, glabella tap, tremor, and salivation. The range of scores is from 0 to 40 with increased scores indicating increased severity.

11.11 Barnes Rating Scale for Akathisia

The Barnes Rating Scale for akathisia is a rating scale used to assess the severity of drug-induced akathisia, or restlessness, involuntary movements, and inability to sit still. The range of scores is 0 to 14, with higher scores indicating greater severity.[23]

11.12 Abnormal Involuntary Movement Scale

The AIMS is a rating scale that is used to measure involuntary movements know as tardive dyskinesia, which can sometimes develop as a side effect of long-term treatment with antipsychotic medications. It is a 12-item scale to assess orofacial, extremity, and truncal movements as well as the overall severity, incapacitation, and the subject's level of awareness of the movements. Items are scored from 0 (none) to 4 (severe). A higher score indicates more severe dyskinesia.

11.13 Columbia-Suicide Severity Rating Scale

The C-SSRS is a tool designed to systematically assess and track suicidal AEs (suicidal behavior and suicidal ideation) throughout the study.[24] The strength of this suicide classification system is in its ability to comprehensively identify suicidal events while limiting the over-identification of suicidal behavior. The scale takes approximately 5 minutes to administer. The C-SSRS will be administered by a trained rater at the site.

11.14 Functional Constipation Inquiry

Constipation refers to bowel movements that are infrequent or hard to pass.[25] The stool is often hard and dry.[26] Other symptoms may include abdominal pain, bloating, and feeling as if one has not completely passed the bowel movement.[27] The normal frequency of bowel movements in adults is between 3 per day and 3 per week.[25] Constipation will be defined per the Rome III criteria, as less than 3 bowel movements per week, Appendix 2 (Longswreth,1486,C3).[28]

The Bristol Stool Form Scale has been correlated with a change in intestinal function, and has been shown to be a useful tool in clinical practice and research.[29] A sample Bristol Stool Form Scale is located in Appendix 2.

As a measure of anticholinergic effects, at specified visits (Table 2), subjects will be asked whether they have experienced constipation per the ROME III criteria since the last visit, and if yes, whether the constipation required intervention. If the subject answers yes, sites are instructed to ask subjects to provide event date and ensure event is documented as an AE and treatment is documented as concomitant medication. Subjects will not be required to collect and present their stool sample, nor will clinic staff be required to corroborate the subject assessment.

Additional attention can be given to other complaints as well including: straining with bowel movements, excessive time needed to pass a bowel movement, hard stools, pain with bowel movements secondary to straining, abdominal pain, abdominal bloating, and the sensation of incomplete bowel evacuation.[27, 30]

Treatment of constipation depends on the underlying cause and the duration that it has been present. For the purposes of constipation complaints during a clinical trial, the use of laxatives of a bulk forming agent, osmotic agent, stool softener, or lubricant type may be used.

As definitions of constipation are typically based on a history of at least a week, site physician discretion will be allowed for initiation of such treatments.

12 EFFICACY ASSESSMENTS

The Schedule of Assessments (Table 2) outlines the efficacy assessments to be performed throughout the study and their timing.

12.1 Positive and Negative Syndrome Scale

The PANSS is a clinician-administered scale used for measuring symptom severity of subjects with schizophrenia and is widely used in the study of antipsychotic therapy.[31] The PANSS rating form contains 7 positive symptom scales, 7 negative system scales, and 16 general psychopathology symptom scales. Subjects are rated from 1 to 7 on each symptom scale. The positive symptoms in schizophrenia are the excess or distortion of normal function such as hallucinations, delusions, grandiosity, and hostility, and the negative symptoms in schizophrenia are the diminution or loss of normal functions. It takes approximately 45 to 50 minutes to administer. PANSS total score is the sum of all scales with a minimum score of 30 and a maximum score of 210.

It is recommended, if at all possible, that the PANSS assessment should be performed before all the other scale assessments for all visits at which it is performed.

12.2 Clinical Global Impression-Severity

The CGI-S is a rating scale, completed independently by a clinician that is used to measure illness and symptom severity in subjects with mental disorders. It is used to rate the severity of a subject's illness at the time of assessment. The CGI-S modified asks the clinician 1 question: *"Considering your total clinical experience, how mentally ill is the subject at this time?"* The clinician's answer is rated on the following 7-point scale: 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill subjects.[32]

This rating is based upon observed and reported symptoms, behavior, and function in the past 7 days. As symptoms and behavior can fluctuate over a week, the score should reflect the average severity level across the 7 days.

13 PHARMACOKINETICS

13.1 Pharmacokinetic Sampling

13.1.1 PK Blood Samples and Timing

On Days 8, 14, 84, 168, and 280, a single sample will be collected during the subject's regularly scheduled study visit (see Table 2). On Day 8 the PK sample should be drawn within 1 to 2 hours post-dose whenever possible.

Approximately 4 mL of blood will be collected at each scheduled time point. The actual date and time of each blood sample collection will be recorded.

A single PK sample may be drawn if a relevant/significant AE is reported or if there is a dose adjustment. For ET that is related to an AE, collection of PK blood sample at the ET visit is recommended.

Details of PK blood sample collection, processing, storage, and shipping procedures will be provided in a separate laboratory manual.

13.2 Pharmacokinetic Analytical Methodology

The plasma concentration of trospium and xanomeline in PK samples will be measured using a validated bioanalytical method. Details of the method validation and sample analysis will be included with the final clinical study report.

14 EXPLORATORY ASSESSMENTS

The exploratory assessments cognition testing, prolactin levels, digital biomarkers, EMA PRO, and EMA VLMT will be performed at scheduled visits or study days, as per the Schedule of Assessments (Table 2).

14.1 Cognition Testing - Cambridge Neuropsychological Test Automated Battery

The computerized CANTAB provides an objective measure of cognitive function correlated to neural networks. A short cognitive battery measuring core cognitive domains of impairment in schizophrenia (ie, as per Brief Assessment of Cognition Schizophrenia key cognitive domains) will be employed for this study, and it will take approximately 30 minutes to complete. These CANTAB tests meet MATRICS workshop criteria.[33] Subjects will perform the test on a provisioned iPad with data immediately uploaded to the CANTAB Connect cloud-based platform (Wi-Fi permitting).

Cognition testing should not be done within 8 hours of receiving benzodiazepine or sleep medications.

Table 6. Cognitive Tests and Cognitive Domains Assessed by the Cambridge Neuropsychological Test Automated Battery

CANTAB Tests	MATRICS Cognitive Domain	Outcome Measures
Rapid visual information processing	Sustained attention/vigilance	**A' Prime:** Signal detection measure of how good the subject is at detecting the target sequence (string of three numbers); regardless of response tendency
Verbal recognition memory	Verbal memory and new learning	**Free Recall:** The total number of words that are correctly recalled from the presentation phase by the subject during the immediate free recall stage
Spatial Span	Working memory	**Forward Span Length:** The longest sequence of boxes successfully recalled by the subject
One-touch stockings of Cambridge	Executive Function Planning/Problem Solving	**Problems Solved on First Choice:** The total number of assessed trials where the subject chose the correct answer on their first attempt

6. Abbreviation: CANTAB = Cambridge Neuropsychological Test Automated Battery

14.2 Change in Prolactin

Blood samples to assess the change in prolactin levels will be obtained on scheduled visits as specified in Table 2. Prolactin sample is optional when sites are using local labs.

14.3 Digital Biomarkers of Schizophrenia (US only)

Study subjects may be performing brief smartphone-based assessments using the AiCure application mentioned in Section 10.2.1. Video and audio of participant behavior captured during these assessments will be used to calculate visual and auditory markers of schizophrenia symptomatology. These digital biomarkers will be used as exploratory efficacy endpoints to measure change from baseline in disease severity. The following exploratory endpoints will be collected:

- Overall emotional expressivity
- Positive emotional expressivity
- Negative emotional expressivity
- Audio intensity / speech volume Fundamental frequency of voice
- Formant frequencies of voice
- Vocal jitter
- Vocal shimmer
- Pause lengths during speech
- Lexical diversity
- Rate of speech
- Euclidean head movement
- Rotational head movement

The collection of digital biomarkers via the AiCure application is optional for all subjects.

14.4 EMA Wellness Assessments

14.4.1 EMA Wellness – EMA PRO (US only)

EMA is an ambulatory data collection technique that allows the real-time in vivo assessment of functioning behaviors. In the present study, EMA Patient Reported Outcomes (PRO) may be used to assess the subject's functioning associated to negative symptoms and psychotic symptoms in schizophrenia through the use of smartphones for subjects enrolled at US sites only.

EMA PRO surveys are multiple choice questions about the subject's current location, if they are alone or with others, and activities and moods in the last hour. A pop-up visualization will signal participants, 3 times per day for 7 days, to respond to very brief (e.g., 3 minutes) questionnaires about their activities, mood, and symptom experiences during the last hour, per the Schedule of Assessments (Table 2). An abbreviated EMA PRO survey, collecting only information on the subject's location, alone or with others, and activities and moods will be given 3 times per day for 3 days starting on Day 4 and Day 15. Daily assessment times will be adjusted to accommodate each subject's typical sleep and wake schedules. The collection of EMA Wellness variables via the EMA PRO application is optional for all subjects.

14.4.2 EMA Wellness - VLMT (US only)

Cognitive insight assessment will be conducted through testing on the Verbal Learning and Memory Test (VLMT), which will be completed by subjects enrolled at US sites only. This assessment will be performed at home on a cellular device 1 time per day for 2 days every 28 days beginning on Day 32. During each VLMT administration, subjects will be presented with a list of 6- or 12-words over in 2 separate trials each lasting 30 seconds. Immediately following each exposure to the list, subjects will be shown target and recognition foil words one-by-one and asked to indicate whether or not the word appeared on the list.

In order to examine response bias and the ability to self-evaluate memory performance, immediately after each recognition trial, the subjects will be asked to indicate how many words they believe that they got correct. They will also be asked how well they did as compared to the previous trial and at the end of the 2 trials they will be asked if they improved over the 2 learning trials.

The collection of EMA Wellness VLMT is optional for all subjects.

14.4.3 Data Collected on EMAW Platform

Data are encrypted and uploaded to secure servers whenever the phone is connected to Wi-Fi or if cellular data is available. If a Wi-Fi and cellular data are unavailable, EMA response data will be transferred during in-clinic visits.

During each EMA PRO, subjects will be asked about their location (home vs away and where if away); they will also be asked if they are alone or with others, and about their activities, symptoms of schizophrenia, and moods in the last hour.

Data collected during the VLMT include the identification of target words and rejections of foils. The participants will also provide an immediate estimate of their memory task performance as soon as each recognition trial is over.

15 STATISTICAL ANALYSIS

A statistical analysis plan (SAP) will be prepared after the protocol is approved. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. The SAP will serve as a complement to the protocol and supersedes it in case of differences.

The statistical evaluation will be performed using SAS® software version 9.4 or higher (SAS Institute, Cary, NC). All data will be listed, and summary tables will be provided. Summary statistics will be presented by dose group. For continuous variables, data will be summarized with the number of subjects (N), mean, standard deviation, median, minimum, and maximum by treatment group. For categorical variables, data will be tabulated with the number and proportion of subjects for each category by treatment group. No statistical hypothesis testing will be performed.

15.1 Determination of Sample Size

As the primary objective of this study is to assess the long-term safety and tolerability of KarXT, the number of subjects anticipated is based on the number of subjects recruited into and completing the acute studies (KAR-007, KAR-009) and meeting the eligibility requirements for KAR-008.

15.2 Analysis Populations

Enrolled population: All subjects who have given informed consent for KAR-008.

Safety population: All subjects who receive at least 1 dose of KarXT during the current study will be included in the safety population and will be used in the safety analysis.

Modified ITT (mITT) population: All subjects who are enrolled, received at least 1 dose of KarXT, and have a valid post-baseline PANSS assessment will be included in the mITT population and will be used in the efficacy analysis.

PK population: All subjects who have received at least 1 dose of KarXT and have at least 1 measurable plasma concentration of KarXT will be included in the PK population.

15.3 Safety Analysis

Safety endpoints will be summarized for all subjects in the Safety population. The presentation of safety data will be based on the treatment received in KAR-008.

All reported AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.1 or higher. The incidence of TEAEs (defined as events with an onset date on or after the first dose of KarXT) will be summarized by System Organ Class and Preferred Term. All AEs will be listed by subject, along with information regarding onset, duration, relationship and severity to KarXT, action taken with KarXT, treatment of event, and outcome.

Orthostatic vital signs, clinical laboratory data, ECG parameters, and physical examinations will be summarized using descriptive statistics, including observed and change from baseline values, as well as numbers of subjects with values outside limits of the normal range at each time point. Similar descriptive summaries will be provided for C-SSRS, SAS, BARS, AIMS, body weight, BMI, and waist circumference.

15.4 Efficacy Analysis

Efficacy analyses will be summarized based on the mITT population. The summaries described in this section will provide data on maintenance of effect of open-label KarXT over 52 weeks. As these variables are summarized over time and the initial values can be impacted by the treatment received in the acute study, the presentation will use a combination of acute/extension study treatment groups, which is intended to provide perspective on the change in these values from the acute study through the treatment period of KAR-008. Tabular presentations will display descriptive statistics for Baseline of the acute study and the observed and change from baseline study results by scheduled visit for KAR-008.

Responder efficacy variables (PANSS responders) will be summarized descriptively. Response will be derived relative to the acute study Baseline assessment.

Continuous efficacy variables based on the change from baseline (PANSS, CGI-S) will be summarized using descriptive statistics by scheduled visit. Tabular presentations will display descriptive statistics for the Baseline of the acute study and the observed and change from baseline results by scheduled visit for KAR-008. Figures for selected variables will also be generated in order to demonstrate the kinetics of response over time.

15.5 Pharmacokinetic Analysis

The PK evaluation will rely on an existing population PK model for KarXT in subjects with schizophrenia. The plasma concentrations of xanomeline and trospium measured in this study will be overlaid onto distributions of concentrations predicted by the population PK model developed from KAR-007 and KAR-009 data. Percentages of measured concentrations in the current study that lie within, above, and below the 90% prediction interval of concentrations predicted by the model will be calculated.

Details of the PK analysis will be described in the SAP.

15.6 Exploratory Analysis

The following will be summarized using descriptive statistics: change in cognition using CANTAB; prolactin levels, digital biomarkers of schizophrenia; EMA PRO and EMA VLMT.

Further details will be provided in the SAP.

15.7 Interim Analysis

No interim analysis is planned for this study.

15.8 Handling of Missing Data

For continuous efficacy variables based on the change from baseline (PANSS, CGI-S), summaries will be based on observed case data.

Additional methods of missing data imputation may be explored and will be outlined in the SAP.

16 STUDY MANAGEMENT

16.1 Approval and Consent

16.1.1 Regulatory Guidelines

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the US Code of Federal Regulations (CFR), in compliance with International Council for Harmonisation (ICH) and good clinical practice (GCP) guidelines, and all applicable local, state and federal government regulations and laws.

16.1.2 Institutional Review Board/Independent Ethics Committee

Conduct of the study must be approved by an appropriately constituted IEC/IRB. Approval is required for the study protocol, protocol amendments (if applicable), IB, ICFs, recruitment material and subject information sheets and other subject-facing material.

16.1.3 Informed Consent

For each study subject, written informed consent will be obtained before any protocol-related activities. As part of this procedure, the PI or designee must explain orally and in writing the nature of the study, its purpose, procedures, expected duration, alternative therapy available, and the benefits and risks involved in study participation. The subject should be informed that they may withdraw from the study at any time, and the subject will receive all information that is required by local regulations and guidelines for ICH. The PI will provide the Sponsor or its representative with a copy of the IEC-/IRB-approved ICF before the start of the study.

The ICF should be revised whenever there are substantial changes to procedures or when new information becomes available that may affect the willingness of the subject to participate. Revisions to the consent form required during the study must be approved by the Sponsor and IEC/IRB, and a copy of the revised consent form is provided to the Sponsor. For any updated or revised consent forms, the subjects must be re-consented for continued participation in the study.

A pregnant partner consent form should be obtained before collecting any data from a female pregnant partner of a male subject, if she becomes pregnant during the course of the study or within 1 week of the last dose of KarXT.

A caregiver consent must be obtained (Ukraine only) before collecting any data from a caregiver pertaining to him or her and the subject.

Subject Registry (US only)

Clinical trial registries, such as clinical trial subject database (CTSdatabase) and Verified Clinical Trials (VCT) seek to reduce duplicate enrollment by identifying potential protocol violations and duplicate subjects before randomization. At the time of providing the informed consent for the initial KAR-007 or -009 study (US Only), the investigator or designee will have

explained the IRB/IEC-approved Subject Database Authorization to the subject and witnessed the signature. That executed authorization form remains in effect for KAR-007 and KAR-008 or KAR-009 and KAR-008 study participation.

At the beginning of screening for KAR-007 or KAR-009 (US only), following consents execution and subject number assignment and before other study procedures, site staff that had received training and login information access (www.subjectregistry.com) to the database entered the subject study ID number and authorized subject identifiers. Two reports, one from CTS and one from VCT, detailing any potential protocol violations or dual enrollment attempts were generated and were printed for source documentation. The reports detailed each protocol violation detected and specific washout period dates where applicable.

Throughout the initial KAR-007 or KAR-009 study, and during this open label extension study, tracking of actively enrolled subjects will continue based on updates by coordinators in the interactive response system. At the last subject contact, CTSdatabase and VCT staff will automatically close out the subject (safety follow-up, ET, or completer) based on interactive response system (IXRS).

16.2 Data Handling

Any data to be recorded directly on the eCRFs (to be considered as source data) will be identified at the start of the study. Data reported on the eCRF that are derived from source documents should be consistent with the source documents, or the discrepancies must be explained. See also Section 16.3.

Clinical data will be entered by site personnel on eCRFs for transmission to the Sponsor. Data on eCRFs transmitted via the web-based data system must correspond to and be supported by source documentation maintained at the study site unless the study site makes direct data entry to the databases for which no other original or source documentation is maintained. In such cases, the study site should document which eCRFs are subject to direct data entry and should have in place procedures to obtain and retain copies of the information submitted by direct data entry. All study forms and records transmitted to the Sponsor must only include coded identifiers such that directly identifying personal information is not transmitted. The primary method of data transmittal is via the secure, internet-based electronic data capture (EDC) system maintained by Syneos Health. Access to the EDC system is available to only authorized users via the study's secure internet web site, where a user unique assigned username and password are required for access.

Any changes made to data after collection will be made through the use of the EDC system. Electronic CRFs will be considered complete when all missing and/or incorrect data have been resolved.

16.3 Source Documents

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. The investigator will provide direct access to source documents and/or source data in the facilitation of trial-related monitoring, audits, review by IECs/IRBs, and regulatory inspections.

The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, not obscure the original entry, and be explained if necessary.

Data recorded on source documents will be transcribed onto eCRFs. Copies of completed eCRFs will be provided to the Sponsor and the sites at the end of the study. The completed eCRFs will be retained by the investigator.

16.4 Record Retention

Study records and source documents must be preserved for at least 15 years after the completion or discontinuation of/withdrawal from the study, at least 2 years after the drug being studied has received its last approval for sale, or at least 2 years after the drug development has stopped, and in accordance with the applicable local privacy laws, whichever is the longer time period.

The investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of subject health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR, Parts 160 and 164 (the HIPAA of 1996 Privacy Regulation). The investigator shall ensure that study subjects authorize the use and disclosure of protected health information in accordance with HIPAA Privacy Regulation and in a form satisfactory to the Sponsor.

16.5 Monitoring

The study will be monitored according to the KAR-008 monitoring plan to ensure that it is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements.

Monitoring visits may include on-site or remote visits and may also utilize periodic telephone contacts. The PI will assure they and adequate site personnel are available throughout the study to collaborate with clinical monitors. Clinical monitors must have direct access to source documentation in order to check the completeness, clarity, and consistency of the data recorded in the eCRFs for each subject.

The investigator will make available to the clinical monitor all source documents and medical records necessary to review protocol adherence and eCRFs. In addition, the investigator will work closely with the clinical monitor and as needed, provide them appropriate evidence that the

study is being conducted in accordance with the protocol, applicable regulations, and GCP guidelines.

16.6 Quality Control and Quality Assurance

The Sponsor or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, security, and reliability of the study data presented to the Sponsor lies with the investigator generating the data.

The Sponsor or its designee will arrange audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the protocol, standard operating procedures, GCP, and all applicable regulatory requirements. Audits will be independent of and separate from the routine monitoring and quality control functions. Quality assurance procedures will be performed at study sites and during data management to assure that safety and efficacy data are adequate and well documented.

16.7 Protocol Amendment and Protocol Deviation

16.7.1 Protocol Amendment

Amendments to the protocol that entail corrections of typographical errors, clarifications of confusing wording, changes in study personnel, and minor modifications that have no effect on the safety of subjects or the conduct of the study will be classed as administrative amendments and will be submitted to the IEC/IRB for information only. Syneos Health will ensure that acknowledgement is received and filed. Amendments that are classed as substantial amendments must be submitted to the appropriate regulatory authorities and the IECs/IRBs for approval and will not be implemented at sites until such approvals are received, other than in the case of an urgent safety measure.

16.7.2 Protocol Deviations

Should a protocol deviation occur, the Sponsor must be informed as soon as possible. Protocol deviations and/or violations and the reasons they occurred will be included in the clinical study report. Reporting of protocol deviations to the IEC/IRB and in accordance with applicable regulatory authority mandates is an investigator's responsibility.

> All protocol deviations will be tracked in the Clinical Trial Management System. Deviations considered major will be identified as such before study unblinding during medical monitor periodic review.

Major protocol deviations will be tabulated including the frequency and percentage of subjects with each type of deviation by treatment group.

16.8 Ethical Considerations

This study will be conducted in accordance with this protocol, the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the CFR; and in compliance with GCP guidelines.

IECs/IRBs will review and approve this protocol and the ICF. All subjects and/or caregivers (Ukraine only) are required to give written informed consent before participation in the study.

16.9 Financing and Insurance

Before the study commences, the Sponsor (or its designee) and the investigator (or the institution, as applicable) will agree on costs necessary to perform the study. This agreement will be documented in a financial agreement that will be signed by the investigator (or the institution signatory) and the Sponsor (or its designee).

The investigator is required to have adequate current insurance to cover claims for negligence and/or malpractice (US only). The Sponsor will provide no-exclusion insurance coverage for the clinical study as required by national regulations.

16.10 Publication Policy/Disclosure of Data

Both the use of data and the publication policy are detailed within the clinical study agreement. Intellectual property rights (and related matters) generated by the investigator and others performing the clinical study will be subject to the terms of a clinical study agreement that will be agreed between the institution and the Sponsor or their designee. With respect to such rights, the Sponsor or its designee will solely own all rights and interests in any materials, data, and intellectual property rights developed by investigators and others performing the clinical study described in this protocol, subject to the terms of any such agreement. In order to facilitate such ownership, investigators will be required to assign all such inventions either to their institution or directly to the Sponsor or its designee, as will be set forth in the clinical study agreement.

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18 APPENDICES

Appendix 1: Contraception Guidelines

Female subjects of childbearing potential with a non-sterilized male sexual partner must agree to use at least 1 highly effective method of contraception beginning >30 days before receiving study drug on Day 1 and continuing until 30 days after the End of Study (EOS) Visit. If oral contraceptives are used, the subject must have been on a stable dose for ≥6 months.

A woman is considered to be WOCBP following menarche and until becoming postmenopausal, unless she is permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy [22]. Female subjects who are postmenopausal, which is defined as 12 consecutive months with no menses without an alternative medical cause, must have been postmenopausal for >1 year if they wish to not use contraceptives. Postmenopausal status must be confirmed by a test of the subject's follicle-stimulating hormone (FSH) level which must be elevated and consistent with postmenopausal levels (ie, >40 IU/L); otherwise, these subjects must agree to use contraceptives listed below. Female subjects who are surgically sterile (ie, hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) will not need to undergo the FSH level test.

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

Highly effective methods of contraception are those that have a failure rate of <1% (when implemented consistently and correctly) and include the following:

- combined (containing estrogen and progestogen) hormonal contraception associated with inhibition of ovulation (administration may be oral, intravaginal, or transdermal)
- progestogen-only hormonal contraception associated with inhibition of ovulation (administration may be oral, injectable, or implantable)
- intrauterine device
- intrauterine hormone-releasing system
- bilateral tubal ligation or occlusion
- vasectomy (provided that the male has a medical assessment of surgical success)

All subjects will be strongly advised that they (or the female partners of male subjects) should not become pregnant before receiving study drug on Day 1 and continuing until 30 days after the End of Study Visit. A female subject will be advised that she must report immediately to the study site for pregnancy testing and appropriate management in the event that she may be pregnant.

Appendix 2: Functional Constipation Inquiry